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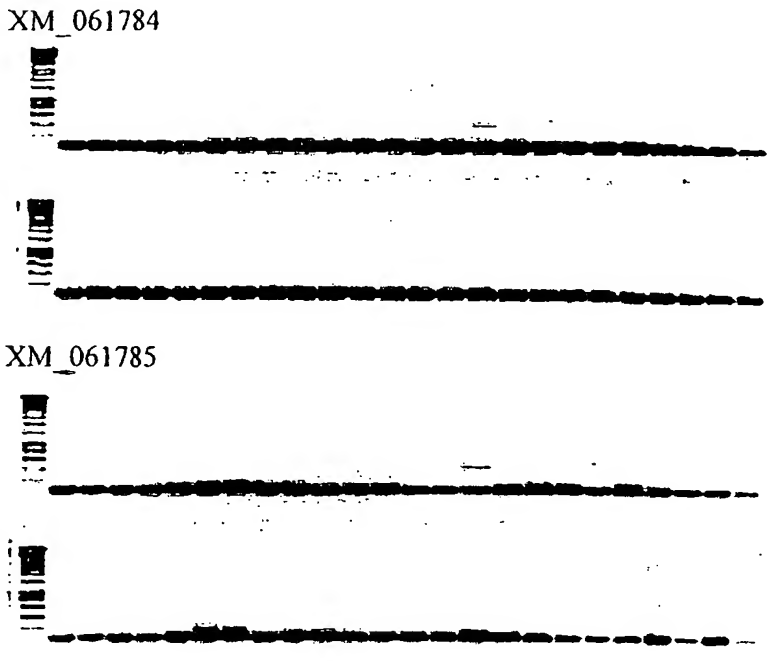
(54) Title: TISSUE SPECIFIC GENES AND GENE CLUSTERS



(57) Abstract: The present invention relates to genes and genes clusters which are expressed in a tissue specific manner. For example, the invention relates to a group of genes encoding GPCR-like receptors that are involved in the function and activity of the immune system. These genes are organized into a discrete cluster at chromosomal location 1q22 (the "immune gene complex") and span about 700 kb of DNA. The region closest to the centromere comprises genes that are expressed predominantly in the thymus, while the distal region comprises genes which are expressed predominantly in the bone marrow and other hematopoietic cells. Another cluster of GPCR genes is located at chromosomal band 11q24. These genes are expressed predominantly in pancreatic tissue, establishing this region of chromosome 11 as a unique gene complex involved in pancreatic function. A cluster of transmembrane and GPCR-type receptor genes is also located at chromosomal band 11q12.2. These genes are expressed predominantly in the spleen (hence, "spleen gene" cluster), as well as other tissues of the immune and reticuloendothelial system (RES), indicating that establishing this region of the chromosome is involved is spleen, lymphoid, and/or reticuloendothelial function. Finally, genes coding for membrane proteins have been identified which are expressed selectively in bone marrow, kidney, pancreas, and retina.

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TISSUE SPECIFIC GENES AND GENE CLUSTERS

This application claims the benefit of U.S. Application Serial Nos. 60/372,669 April 16, 2002, 60/374,823 filed April 24, 2002, 60/376,558 filed May 1, 2002, 60/381,366 filed May 20, 2002, 60/403,648 filed August 16, 2002, 60/411,882 filed September 20, 2002, and 60/424,336 filed November 7, 2002, which are hereby incorporated by reference in their entirety.

DESCRIPTION OF THE DRAWINGS

Figs. 1 and 2 show a physical map of the immune system gene complex. Sequence-tagged site ("STS") markers are used to characterize the chromosomal regions. An STS is defined by two short synthetic sequences (typically 20 to 25 bases each) that have been designed from a region of sequence that appears as a single-copy in the human genome (the reference numbers, and the sequences which they represent, are hereby incorporated by reference in their entirety). These sequences can be used as primers in a polymerase chain reaction (PCR) assay to determine whether the site is present or absent from a DNA sample.

Fig. 3 shows the expression pattern of transmembrane proteins homologous to the olfactory G-protein-coupled receptor ("GPCR") family in human tissues. To detect gene expression, PCR was carried out on aliquots of the normalized tissue samples using a forward and reverse gene-specific primers. Table 5 indicates the SEQ ID NO for each primer ("FOR" is the forward primer and "REV" is the reverse primer).

Fig. 4 shows the expression pattern of two olfactory G-protein-coupled receptor ("GPCR") family members in human tissues. To detect gene expression, PCR was carried out on aliquots of the normalized tissue samples using a forward and reverse gene-specific primers. Table 6 indicates the SEQ ID NO for each primer ("FOR" is the forward primer and "REV" is the reverse primer).

Figs. 5 (a and b) and 6 show the expression pattern in human tissues of genes selectively expressed in kidney tissue. To detect gene expression, PCR was carried out on aliquots of the normalized tissue samples using a forward and reverse gene-specific primers. Table 11 indicates the SEQ ID NO for each primer ("FOR" is the forward primer and "REV" is the reverse primer).

Fig. 7 (a-b) show organization of pancreatic gene complex on chromosome 11q24.

Fig. 8 is a schematic drawing of five of the pancreatic olfactory G-protein-coupled receptor ("GPCR") family members located in the gene complex showing regions of overlap. The numbering underneath the lines indicates amino acid position.

Fig. 9 (a and b) show the expression pattern of TMD0986, XM_061780 (TMD0987), XM_061781 (TMD0353), XM_061784 (TMD0989), and XM_061785 (TMD058) in human tissues. To detect gene expression, PCR was carried out on aliquots of the normalized tissue samples using a forward and reverse gene-specific primers. Table 12 indicates the SEQ ID NO for each primer ("FOR" is the forward primer and "REV" is the reverse primer).

Fig. 10 shows the expression pattern of TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), and TMD0621 (XM_166205) in human tissues. To detect gene expression, PCR was carried out on aliquots of the normalized tissue samples using a forward and reverse gene-specific primers. Table 17 indicates the SEQ ID NO for each primer ("F-oligo" is the forward primer and "R-oligo" is the reverse primer).

Fig. 11 shows the organization of the spleen gene complex on chromosome 11q12.2.

Fig. 12 (a-c) shows the expression of the pancreas genes in human tissues. To detect gene expression, PCR was carried out on aliquots of the normalized tissue samples using a forward and reverse gene-specific primers. Table 23 indicates the SEQ ID NO for each primer ("FOR" is the forward primer and "REV" is the reverse primer).

Expression patterns were analyzed as described below. A twenty-four tissue panel was used (lanes from left to right): 1, adrenal gland; 2, bone marrow; 3, brain; 4, colon; 5, heart; 6, intestine; 7, pancreas; 8, liver; 9, lung; 10, lymph node; 11, lymphocytes; 12, mammary gland; 13, muscle; 14, ovary; 15, pancreas; 16, pituitary; 17, prostate; 18, skin; 19, spleen; 20, stomach; 21, testis; 22, thymus; 23, thyroid; 24, uterus. The lane at the far left of each panel contains molecular weight standards. Polyadenylated mRNA was isolated from tissue samples, and used as a template for first-strand cDNA synthesis. The resulting cDNA samples were normalized using beta-actin as a standard. For the normalization procedure, PCR was performed on aliquots of the first-strand cDNA using beta-actin specific primers. The PCR products were visualized on an ethidium bromide stained agarose gel to estimate the quantity of beta-actin cDNA present in each sample. Based on these estimates, each sample was diluted with buffer until each contained the same quantity of beta-actin cDNA per unit volume. PCR was carried out using the primers described above, and reaction

products were loaded on to an agarose (e.g., 1.5-2%) gel and separated electrophoretically.

DESCRIPTION OF THE INVENTION

The present invention relates to tissue-selective genes and tissue-selective gene clusters. The polynucleotides and polypeptides are useful in variety of ways, including, but not limited to, as molecular markers, as drug targets, and for detecting, diagnosing, staging, monitoring, prognosticating, preventing or treating, determining predisposition to, etc., diseases and conditions, associated with genes of the present invention. The identification of specific genes, and groups of genes, expressed in pathways physiologically relevant to particular tissues, permits the definition of functional and disease pathways, and the delineation of targets in these pathways which are useful in diagnostic, therapeutic, and clinical applications. The present invention also relates to methods of using the polynucleotides and related products (proteins, antibodies, etc.) in business and computer-related methods, e.g., advertising, displaying, offering, selling, etc., such products for sale, commercial use, licensing, etc.

Immune Gene Complex

The present invention relates to a group of genes involved in the function and activity of the immune system. These genes are organized into a discrete cluster at chromosomal location 1q22 (the "immune gene complex") and span hundreds of kb of DNA, e.g., about 700 kb of DNA. See, Figs. 1 and 2. The region closest to the centromere comprises genes that are expressed predominantly in the thymus, while the distal region comprises genes which are expressed predominantly in the bone marrow and other hematopoietic cells.

The present invention relates to a composition consisting essentially of the 1q22 immune gene complex, comprising TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959) genes, or a fragment thereof comprising at least two said genes. As discussed in more detail, the composition can comprise or consist essentially of the chromosome region between STS markers that define the genomic DNA, e.g., between SHGC-81033 and SHGC-145403, or a fragment thereof comprising at least two said genes.

The CD1 family, a cluster of genes previously identified as coding for proteins involved in antigen presentation (Sugita and Brenner, Seminars in Immunology, 12:511-516, 2000), are located at the proximal boundary of the immune gene complex. The expression of CD1a, b, and c genes are restricted to professional antigen-presenting cells, including dendritic cells and some B-cell subsets (Sugita and Brenner, ibid). CD1d is present on other cell types, in addition to hematopoietic cells, such as intestinal cells (Sugita and Brenner, ibid).

Adjacent to the CD1 family, is a cluster of genes coding for transmembrane proteins homologous to the olfactory G-protein-coupled receptor ("GPCR") family. These genes include XM_060945 (TMD0024), XM_060346 (TMD1779), XM_060947 (TMD0884), and XM_060948 (TMD0025), and are expressed predominantly in thymus tissues (e.g., thymocytes). XM_089421 (TMD1781) is also expressed in thymus, but it is present in much higher amounts in lymphocytes ("PBL"). This chromosomal region can be defined by STS markers, e.g., between SHGC-81033 and D1S3249, G15944, GDB:191077, GDB:196442, RH68459, RH102597, RH69635, or RH65132, or fragments thereof, such as fragments which comprise two or more genes.

The gene for human erythroid alpha spectrin (SPTA1) is distal to the GPCR thymus-restricted family. It is expressed in bone marrow cells, and is localized to the red cell membrane (Wilmotte et al., Blood, 90(10):4188-96, 1997). Next to it, is another cluster of genes coding for proteins that resemble the olfactory GPCR family. These include XM_060956 (TMD0304), XM_060957 (TMD0888), and XM_060959 (TMD089), and are expressed predominantly in the bone marrow, although other sites of expression are observed as well. See, e.g., Table 1. This chromosomal region can be defined by STS markers, e.g., between GDB:181583 or RH118729, and D1S2577 or SHGC-145403.

The gene for myeloid cell nuclear differentiation antigen ("MNDA") is next. MNDA is also expressed in bone marrow cells, particularly in normal and neoplastic myelomonocytic cells and a subset of normal and neoplastic B lymphocytes (Miranda et al., Hum. Pathol., 30(9):1040-9, 1999).

The phrase "immune system" indicates any processes and cells which are involved in generating and carrying out an immune response. Immune system cells includes, but are not limited to, e.g., stem cells, pluripotent stem cell, myeloid progenitor, lymphoid progenitor,

lymphocytes, B-lymphocytes, T-lymphocytes (e.g., naive, effector, memory, cytotoxic, etc.), thymocytes, natural killer, erythroid, megakaryocyte, basophil, eosinophil, granulocyte-monocyte, accessory cells (e.g., cells that participate in initiating lymphocyte responses to antigens), antigen-presenting cells ("APC"), mononuclear phagocytes, dendritic cells, macrophages, alveolar macrophages, etc., and any precursors, progenitors, or mature stages thereof.

Table 1 is a summary of the genes and their expression patterns in accordance with the present invention. The genes and the polypeptides they encode can be used as diagnostic, prognostic, therapeutic, and research tools for any conditions, diseases, disorders, or applications associated with the tissues and cells in which they are expressed.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold, etc., or more) in that tissue when compared to other tissue-types.

In view of their selectivity and display on the cell surface, the olfactory GPCR family members of the present invention are a useful target for histological, diagnostic, and therapeutic applications relating to the cells in which they are expressed. Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging, therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such as antibodies, can be used to treat carcinomas in analogy to how c-erbB-2 antibodies are used to breast cancer. They can also be used to detect metastatic cells, in biopsies to identify bone marrow and thymus tissue, etc. The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or other binding partners include those that are specific for parts of the

polypeptide which are exposed extracellularly as indicated in Table 2. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo (e.g., bone marrow cells or peripheral blood lymphocytes can be treated ex vivo and then returned to the body).

The expression patterns of the selectively expressed polynucleotides disclosed herein can be described as a "fingerprint" in that they are a distinctive pattern displayed by a tissue. Just as with a fingerprint, an expression pattern can be used as a unique identifier to characterize the status of a tissue sample. The list of expressed sequences disclosed herein provides an example of such a tissue expression profile. It can be used as a point of reference to compare and characterize samples. Tissue fingerprints can be used in many ways, e.g., to classify an unknown tissue, to determine the origin of metastatic cells, to assess the physiological status of a tissue, to determine the effect of a particular treatment regime on a tissue, to evaluate the toxicity of a compound on a tissue of interest, etc.

For example, the tissue-selective polynucleotides disclosed herein represent the configuration of genes expressed by a normal tissue. To determine the effect of a toxin on a tissue, a sample of tissue can be obtained prior to toxin exposure ("control") and then at one or more time points after toxin exposure ("experimental"). An array of tissue-selective probes can be used to assess the expression patterns for both the control and experimental samples. As discussed in more detail below, any suitable method can be used. For instance, a DNA microarray can be prepared having a set of tissue-selective genes arranged on to a small surface area in fixed and addressable positions. RNA isolated from samples can be labeled using reverse transcriptase and radioactive nucleotides, hybridized to the array, and then expression levels determined using a detection system. Several kinds of information can be extracted: presence or absence of expression, and the corresponding expression levels. The normal tissue would be expected to express substantially all the genes represented by the tissue-selective probes. The various experimental conditions can be compared to it to determine whether a gene is expressed, and how its levels match up to the normal control.

While the expression profile of the complete gene set represented by the sequences disclosed here may be most informative, a fingerprint containing expression information from less than the full collection can be useful, as well. In the same way that an incomplete fingerprint may contain enough of the pattern of whorls, arches, loops, and ridges, to identify

the individual, a cell expression fingerprint containing less than the full complement may be adequate to provide useful and unique identifying and other information about the sample. Moreover, because of heterogeneity of the population, as well differences in the particular physiological state of the tissue, a tissue's "normal" expression profile is expected to differ between samples, albeit in ways that do not change the overall expression pattern. As a result of these individual differences, each gene although expressed selectively in spleen, may not on its own 100% of the time be adequately enough expressed to distinguish said tissue. Thus, the genes can be used in any of the methods and processes mentioned above and below as a group, or one at a time.

Binding partners can also be used as to specifically deliver therapeutic agents to a tissue of interest. For example, a gene to be delivered to a tissue can be conjugated to a binding partner (directly or through a polymer, etc.), in liposomes comprising cell surface, and then administered as appropriate to the subject who is to be treated. Additionally, cytotoxic, cytostatic, and other therapeutic agents can be delivered specifically to the tissue to treat and/or prevent any of the conditions associated with the tissue of interest.

The present invention relates to methods of detecting immune system cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for a gene selected from Table 1, or a mammalian homolog thereof, under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization. Detecting can be accomplished by any suitable method and technology, including, e.g., any of those mentioned and discussed below, such as Northern blot and PCR. Specific polynucleotides include SEQ ID NOS 3, 4, 8, 9, 14, 15, 22, 23, 27, 28, 35, 36, 42, 43, 49, 50, 57, and 58 (see, Table 5), and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g., monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting an immune system cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by gene selected from Table 1 , or a mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding assays can be

accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface as indicated in Table 2.

As indicated above, binding partners can be used to deliver agents specifically to the immune system, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of delivering an agent to an immune cell can comprise, e.g., contacting an immune cell with an agent coupled to binding partner specific for a gene selected from Table 1 (i.e., TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959)), whereby said agent is delivered to said cell. Any type of agent can be used, including, therapeutic and imaging agents. Contact with the immune system can be achieved in any effective manner, including by administering effective amounts of the agent to a host orally, parentally, locally, systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent is associated with the binding partner in such a manner that it can be carried specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target), present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers.

Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body. Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintographic. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos, 6,264,917, 6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The methods described therein can be used generally to associate a partner with an agent for any desired purpose.

The maturation of the immune system can also be modulated in accordance with the

present invention, e.g., by methods of modulating the maturation of an immune system cell, comprising, e.g., contacting said cell with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from Table 1, or a mammalian homolog thereof, whereby the maturation of an immune cell is modulated. Modulation as used throughout includes, e.g., stimulating, increasing, agonizing, activating, amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.

The phrase "immune system cell maturation" includes indirect or direct effects on immune system cell maturation, i.e., where modulating the gene directly effects the maturational process by modulating a gene in a immune system cell, or less directly, e.g., where the gene is expressed in a cell-type that delivers a maturational signal to the immune system cell. Immune system maturation includes B-cell maturation, T-cell maturation, such as positive selection, negative selection, apoptosis, recombination, expression of T-cell receptor genes, CD4 and CD8 receptors, antigen recognition, MHC recognition, tolerization, RAG expression, differentiation, TCR expression, antigen expression, etc. See also below and, e.g., Abbas et al., *Cellular and Molecular Immunology*, 4th Edition, W.B. Saunders Company, 2000, e.g., Pages 149-160. Process include reception of a signal, such as cytokinin or other GPCR ligand. Any suitable agent can be used, e.g., agents that block the maturation, such as an antibody to a GPCR of Table 1, or other GPCR antagonist.

The interactions between lymphoid and non-lymphoid immune system cells can also be modulated comprising, e.g., contacting said cells with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from Table 1, or a mammalian homolog thereof, whereby the interaction is modulated. Lymphoid cells, includes, e.g., lymphocytes (T- and B-), natural killer cells, and other progeny of a lymphoid progenitor cell. Non-lymphoid cells include accessory cells, such as antigen presenting cells, macrophages, mononuclear phagocytes dendritic cells, non-lymphoid thymocytes, and other cell types which do not normally arise from lymphoid progenitors. Interactions that can be modulated included, e.g., antigen presentation, positive selection, negative selection, progenitor cell differentiation, antigen expression, tolerization, TCR expression, apoptosis. See, also above and below, for other immune system processes.

Promoter sequences obtained from GPCR genes of the present invention can be utilized to selectively express heterologous genes in immune system cells. Methods of

expressing a heterologous polynucleotide in immune system cells can comprise, e.g., expressing a nucleic acid construct in immune system cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected from Table 5. In addition to the cell lines mentioned below, the construct can be expressed in primary cells, such as thymocytes, bone marrow cells, stem cells, lymphoid progenitor cells, myeloid progenitor cells, monocytes, antigen presenting cells, macrophages, and cell lines derived therefom, cell lines such as JHK3 (CRL-10991), KG-1 (CCL-246), KG-1a (CCL-246.1), U-937 (CRL-1593.2), VA-ES-BJ (CRL-2138), TUR (CRL-2367), ELI (CRL-9854), 28SC (CRL-9855), KMA (CRL-9856), THP-1 (TIB-2002), WEHI-274.1 (CRL-1679), M-NFS-60 (CRL-1838), MH-S (CRL-2019), SR-4987 (CRL-2028),NCTC 3749 (CCL-461), AMJ2-C8 (CRL 2455), AMJ2-C11 (CRL2456), PMJ2-PC (CRL-2457), EOC2 (CRL-2467), as well as any primary and established immune system cell lines.

Thymus

The thymus is the site of T-cell lymphocyte maturation. Immature lymphocytes migrate into the thymus from the bone marrow and other organs in which they are generated. The selection process that shape the antigen repertoire of T-cells takes place in the thymus organ. Both positive and negative selection processes take place. For a review, see, e.g., Abbas et al., Cellular and Molecular Immunology, 4th Edition, W.B. Saunders Company, 2000, e.g., Pages 126-130 and 149-160.

There are various diseases and disorders related to thymus tissue, including, but not limited to, thymic carcinoma, thymoma, Omenn syndrome, autoimmune diseases, allergy, Graves disease, Myasthenia gravis, thymic hyperplasia, DiGeorge syndrome, Good syndrome, promoting immune system regeneration after bone marrow transplantation, immuno-responsiveness, etc. The thymic selective genes and polypeptides encoded thereby can be use to treat or diagnose any thymic condition. For instance, chemotherapeutic and cytotoxic agents can be conjugated to thymic selective antibodies and used to ablate a thymoma or carcinoma. They can be used alone or in combination with other treatments. See, e.g., Graeber and Tamin, Semin. Thorac. Cardiovasc. Surg., 12:268-277, 2000; Loehrer, Ann. Med., 31 Suppl. 2:73-79, 1999.

Bone marrow

All circulating blood cells in the adult, including all immature lymphocytes, are produced in the bone marrow. In addition, the bone marrow is also the site of B-cell maturation. The marrow consists of a spongelike reticular framework located between long trabeculae. It is filled with fat cells, stromal cells, and precursor hematopoietic cells. The precursors mature and exit through the vascular sinuses

All the blood cells are believed to arise from a common stem cell. Lineages that develop from this common stem cell include, e.g., myeloid and lymphoid progenitor cells. The myeloid progenitor develops into, erythrocytes (erythroid), platelets (megokaryocytic), basophils, eosinophils, granulocytes, neutrophils, and monocytes. The lymphoid progenitor is the precursor to B-lymphocytes, T-lymphocytes, and natural killer cells.

There are various diseases and disorders related to bone marrow, including, not limited to, e.g., red cell diseases, aplastic anemia (e.g., where there is a defect in the myeloid stem cell), pure red cell aplasia, white cell diseases, leukopenia, neutropenia, reactive (inflammatory) proliferation of white cells and nodes such as leukocytosis and lymphadenitis, neoplastic proliferation of white cells, malignant lymphoma, Non-Hodgkin's Lymphomas, Hodgkins disease, acute leukemias (e.g., acute lymphoblastic leukemia, acute myeloblastic leukemia, myelodysplatic snydrome), chromic myeloid leukemia, chronic leukemia. hairy cell leukemia, myeloproliferative disorders, plasma cell disorders, multiple myeloma, histiocytoses, etc.

Immune System Selective Genes

The present invention relates to genes involved in the function and activity of the immune system. XM_062147 (TMD0088) and XM_061676 (TMD0045) code for seven membrane spanning polypeptides which are homologous to members of the olfactory G-protein-coupled receptor ("GPCR") family. XM_062147 is expressed predominantly in bone marrow tissue, with no detectable expression in other tissues. XM_061676 is also expressed predominantly in bone marrow tissue, but it is detected in peripheral blood lymphocytes, as well. As discussed in more detail below, XM_062147 (TMD0088), XM_061676 (TMD0045), and the polypeptides they encode, can be used as diagnostic, prognostic, therapeutic, and research tools for any conditions, diseases, disorders, or applications

associated with the immune system and the cells in which they are expressed.

In view of their selectivity and display on the cell surface, the GPCR family members of the present invention are useful targets for histological, diagnostic, and therapeutic applications relating to the cells (e.g., B-cells and B-cell progenitors) in which they are expressed. Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging, therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such as antibodies, can be used to treat carcinomas in analogy to how c-erbB-2 antibodies are used to breast cancer. They can also be used to detect metastatic cells, in biopsies to identify bone marrow, lymphocytes, etc. The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or other binding partners include those that are specific for parts of the polypeptide which are exposed extracellularly as indicated in Table 2. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo (e.g., bone marrow cells or peripheral blood lymphocytes can be treated ex vivo and then returned to the body). Ex vivo methods can be used to eliminate cancerous cells from the bone marrow, to modulate bone marrow cells, to prime bone marrow cells for an immune response, to expand a particular class of cells expressing XM_062147 (TMD0088) or XM_061676 (TMD0045), to transfer genes into said cells (e.g., Banerjee and Bertino, *Lancet Oncol.*, 3:154-158, 2002), etc.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold, etc., or more) in that tissue when compared to other tissue-types.

The phrase "immune system" indicates any processes and cells which are involved in

generating and carrying out an immune response. Immune system cells includes, but are not limited to, e.g., stem cells, pluripotent stem cell, myeloid progenitor, lymphoid progenitor, lymphocytes, B-lymphocytes, T-lymphocytes (e.g., naive, effector, memory, cytotoxic, etc.), thymocytes, natural killer, erythroid, megakaryocyte, basophil, eosinophil, granulocyte-monocyte, accessory cells (e.g., cells that participate in initiating lymphocyte responses to antigens), antigen-presenting cells ("APC"), mononuclear phagocytes, dendritic cells, macrophages, etc., and any precursors, progenitors, or mature stages thereof.

XM_062147 contains seven transmembrane segments. It is located on chromosomal band 11q12 within proximity to the locus for an inherited form of atopic hypersenstivity (OMIM 147050, e.g., associated with asthma, hay fever, and eczema). It has been suggested that the condition is a result of defect in the regulation of immunoglobulin E. XM_061676 also is seven membrane spanning polypeptide. The chromosomal locus, 11p15, to which it maps is rich in genes associated with immune disorders, including Fanconi anemia, nucleoporin, myeloid leukemia, and T-cell lymphoblastic leukemia. Arthrogryposis multiplex congenita (distal type IIB) also maps closely to this chromosomal location.

The present invention relates to methods of detecting immune system cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for a gene selected from Table 6, or a mammalian homolog thereof, under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization. Detecting can be accomplished by any suitable method and technology, including, e.g., any of those mentioned and discussed below, such as Northern blot and PCR. Specific polynucleotides include SEQ ID NOS 67, 68, 76, and 77 (see, Table 6), and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g., monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting an immune system cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by gene selected from Table 6, or a mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding assays can be

accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface as indicated in Table 7.

As indicated above, binding partners can be used to deliver agents specifically to the immune system, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of delivering an agent to an immune cell can comprise, e.g., contacting an immune cell with an agent coupled to binding partner specific for a gene selected from Table 6, whereby said agent is delivered to said cell. Any type of agent can be used, including, therapeutic and imaging agents. Contact with the immune system can be achieved in any effective manner, including by administering effective amounts of the agent to a host orally, parentally, locally, systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent is associated with the binding partner in such a manner that it can be carried specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target), present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers.

Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body. Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintographic. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos. 6,264,917, 6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The methods described therein can be used generally to associate a partner with an agent for any desired purpose.

The maturation of the immune system can also be modulated in accordance with the present invention, e.g., by methods of modulating the maturation of an immune system cell, comprising, e.g., contacting said cell with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from Table 6, or a mammalian homolog thereof,

whereby the maturation of an immune cell is modulated. Modulation as used throughout includes, e.g., stimulating, increasing, agonizing, activating, amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.

The phrase "immune system cell maturation" includes indirect or direct effects on immune system cell maturation, i.e., where modulating the gene directly effects the maturational process by modulating a gene in a immune system cell, or less directly, e.g., where the gene is expressed in a cell-type that delivers a maturational signal to the immune system cell. Immune system maturation includes B-cell maturation, T-cell maturation, such as positive selection, negative selection, apoptosis, recombination, expression of T-cell receptor genes, CD4 and CD8 receptors, antigen recognition, MHC recognition, tolerization, RAG expression, differentiation, TCR expression, antigen expression, etc. See also below and, e.g., Abbas et al., *Cellular and Molecular Immunology*, 4th Edition, W.B. Saunders Company, 2000, e.g., Pages 149-160. Processes include reception of a signal, such as cytokinin or other GPCR ligand. Any suitable agent can be used, e.g., agents that block the maturation, such as an antibody to a GPCR of Table 6, or other GPCR antagonist.

The interactions between lymphoid and non-lymphoid immune system cells can also be modulated comprising, e.g., contacting said cells with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from Table 6, or a mammalian homolog thereof, whereby the interaction is modulated. Lymphoid cells, includes, e.g., lymphocytes (T- and B-), natural killer cells, and other progeny of a lymphoid progenitor cell. Non-lymphoid cells include accessory cells, such as antigen presenting cells, macrophages, mononuclear phagocytes dendritic cells, non-lymphoid thymocytes, and other cell types which do not normally arise from lymphoid progenitors. Interactions that can be modulated included, e.g., antigen presentation, positive selection, negative selection, progenitor cell differentiation, antigen expression, tolerization, TCR expression, apoptosis. See, also above and below, for other immune system processes.

Promoter sequences obtained from GPCR genes of the present invention can be utilized to selectively express heterologous genes in immune system cells. Methods of expressing a heterologous polynucleotide in immune system cells can comprise, e.g., expressing a nucleic acid construct in immune system cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said

promoter sequence is selected from Table 6. In addition to the cell lines mentioned below, the construct can be expressed in primary cells, such as thymocytes, bone marrow cells, stem cells, lymphoid progenitor cells, myeloid progenitor cells, monocytes, B-cells, antigen presenting cells, macrophages, and cell lines derived therefrom.

Kidney Selective Genes

The present invention relates to genes and polypeptides which are selectively expressed in kidney tissues: TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108). These genes and polypeptides are expressed predominantly in kidney tissues, making them, and the polypeptides they encode, useful as selective markers for kidney tissue and function, as well as diagnostic, prognostic, therapeutic, and research tools for any conditions, diseases, disorders, or applications associated with the kidney and the cells in which they are expressed. TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108) includes both human and mammalian homologs of it. SEQ ID NOS 78-103 represent particular alleles, but the present invention relates to other alleles, including naturally-occurring polymorphisms (i.e., a polymorphism in the nucleotide sequence which is identified in populations of mammals) and homologs thereof. More information on these genes is summarized in Tables 8-11.

In view of their selectivity and display on the cell surface, the polypeptides and polynucleotides of the present invention are useful targets for histological, diagnostic, and therapeutic applications relating to the cells (e.g., juxtaglomerular cells which secrete renin, peritubular cells, endothelial cells, e.g., of the cortex and outer medulla, mesangial cells which secrete inflammatory mediators including NO and products of cyclooxygenase, visceral epithelial cells, parietal epithelial cells, podocytes, early proximal tubule cells which secrete, e.g., angiotensin converting enzyme and neutral endopeptidase, late distal tubule

cells that produce, e.g., prolyl endopeptidase, serine endopeptidase, carboxypeptidase, and neutral endopeptidase, renomedullary interstitial cells, etc) in which they are expressed. Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging, therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such as antibodies, can be used to treat carcinomas in analogy to how c-erbB-2 antibodies are used to breast cancer. They can also be used to detect metastatic cells, in biopsies, to identify kidney, etc. The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or other binding partners include those that are specific for parts of the polypeptide which are exposed extracellularly as indicated in Table 9. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold, etc., or more) in that tissue when compared to other tissue-types.

The present invention relates to methods of detecting kidney cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108), or a mammalian homolog thereof, under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization. Detecting can be accomplished by any suitable method and technology, including, e.g., any of those mentioned and discussed below,

such as Northern blot and PCR. Specific polynucleotides include SEQ ID NOS 104, 105, 107, 108, 111, 112, 115, 116, 119, 120, 122, 123, 126, 127, 131, 132, 135, 136, 138, 139, 142, 143, 145, 146, 149, 150, and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g., monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting a kidney cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108), or a mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding assays can be accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface as indicated in Table 9.

As indicated above, binding partners can be used to deliver agents specifically to the kidney, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of delivering an agent to a kidney cell can comprise, e.g., contacting a kidney cell with an agent coupled to binding partner specific for TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108), whereby said agent is delivered to said cell. Any type of agent can be used, including, therapeutic and imaging agents. Contact with the kidney can be achieved in any effective manner, including by administering effective amounts of the agent to a host orally, parentally, locally, systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent is associated with the binding partner in such a manner that it can be carried specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target),

present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers. Any cell expressing a polypeptide coded for by TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108) can be targeted, including, e.g., juxtaglomerular, peritubular, endothelial, mesangial, visceral epithelial, parietal epithelial, podocytes, early proximal tubule, late distal tubule, renomedullary interstitial, etc.

Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body. Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintographic. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos, 6,264,917, 6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The methods described therein can be used generally to associate a partner with an agent for any desired purpose.

A kidney cell (see above for examples of kidney cell types) can also be modulated in accordance with the present invention, e.g., by methods of modulating a kidney cell, comprising, e.g., contacting said cell with an agent effective to modulate TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108), or the biological activity of a polypeptide encoded thereby, or a mammalian homolog thereof, whereby said kidney cell is modulated. Modulation as used throughout includes, e.g., stimulating, increasing, agonizing, activating, amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.

An activity or function of the kidney cell can be modulated, including, e.g., glomerular filtration rate, filtration pressure, renal autoregulation (including via myogenic mechanism and tubuloglomerular feedback mechanism), tubular reabsorption, tubular secretion, and renal clearance. In addition, the transcription, translation, synthesis, degradation, expression, etc., of any secretory or polypeptide produced by a kidney cell can be modulated, including, but not limited to, renin-angiotensin activity, production and secretion of prostaglandins, nitric oxide, kallikrein, adenosine, endothelin, erythropoietin, and other hormones, enzymes, and other secretory and intracellular factors. The response of a kidney cell to stimuli can also be modulated, including, but not limited to, ligands to TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108), oxygen levels, blood pressure, etc.

The present invention also relates to polypeptide detection methods for assessing kidney function, e.g., methods of assessing kidney function, comprising, detecting a polypeptide coded for by TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108), fragments thereof, polymorphisms thereof, in a body fluid, whereby the level of said polypeptide in said fluid is a measure of kidney function. Kidney function tests are usually performed to determine whether the kidney is functioning normally as a way of diagnosing kidney disease. Various tests are commonly used, including, e.g., BUN (blood urea nitrogen), serum creatinine, estimated GFR, ability to concentrate urine, BUN/creatine ratio, urine sodium and other electrolytes, urine NAG (N-acetyl-beta-glucosaminidase, adenosine deaminase, urinary alkaline phosphatase, serum and urine beta-2-microglobulin, serum uric acid, isotope scans, Doppler sonogram, positron emission tomography, specific gravity of urine, microalbumin, total protein, etc. Detection of TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148

(XM_087108) provides an additional assessment tool, especially in diseases such as chromic renal failure, urinary tract infections, kidney stones, nephrotic syndrome, nephritic syndrome, kidney disease due to diabetes or high blood pressure, etc., As with the other tests, elevated levels of said polypeptide in blood, or other fluids, can indicate impaired kidney function. Values can be determined routinely, as they are for other kidney function markers, such as those mentioned above. Detecting can be performed routinely (see below), e.g., using an antibody which is specific for said polypeptide, by RIA, ELISA, or Western blot, etc.

Promoter sequences obtained from genes of the present invention can be utilized to selectively express heterologous genes in kidney cells. Methods of expressing a heterologous polynucleotide in kidney cells can comprise, e.g., expressing a nucleic acid construct in kidney cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected SEQ ID NOS 106, 109, 110, 113, 114, 117, 118, 121, 124, 125, 128-130, 133, 134, 137, 140, 141, 144, 147, 148, and 151. In addition to the cell lines mentioned below, the construct can be expressed in primary cells or in established cell lines.

Kidney

The kidney maintains the constancy of fluids in an organism's internal environment, and is therefore of great importance in maintaining health and vitality. Each day, the kidney filters the blood, removing and concentrating toxins, metabolic wastes, and excess ions, allowing them to be excreted by the body in the form of urine. The excretory function of the kidney is performed by over one million blood units called nephrons, each a miniature blood filtering and processing unit. A nephron consists of a glomerulus, a tuft of capillaries, and a renal tubule. In addition to their excretory function, kidneys produce a number of different hormones, enzymes, and other secreted molecules, including the enzyme renin and the hormone erythropoietin. The kidney also is responsible for metabolizing vitamin D into its active form, calcitriol. For a full description of the kidney's function and structure, see, e.g., *Human Anatomy and Physiology*, Marieb, E.N., 3rd Edition, Benjamin/Cummings Publishing Company, Inc., 1995, pp 896-923.

The glomerulus is a high pressure capillary bed which filters out most substances smaller than large plasma proteins across the fenestrated glomerular epithelium, the

intervening basement membrane, and the podocyte-containing visceral membrane of the glomerulus capsule. The external layer of the glomerulus is called the parietal layer, consisting predominaly of a squamous epithelium. This layer is structural. Underneath it, is the visceral layer which consists of the modified branching epithelial cells called podocytes. These sit on top of the fenestratrated glomerular endothelium. The glomerulus is connected to the renal tubule, a highly differentiated and long tube, having three major elements: the proximal convoluted tubule, the loop of Henel, and the distal convoluted tubule. Different regions of the tubule have different functions in absorption and secretion.

Renal cells produce a variety of different hormones and chemicals, including, prostaglandins, nitric oxide, kallikrein family, adenosine, endothelin family, renin, erythropoietin, aldosterone, antidiuretic hormone (vasopressin), natriuretic hormones, etc. Renin is involved in modulating blood pressure. It cleaves angiotensinogen, a plasma peptide, splitting off a fragment containing 10 amino acids called angiotensin I. Angiotensin I is cleaved by a peptidase secreted by blood vessels called angiotensin converting enzyme (ACE), producing angiotensin II, which contains 8 amino acids. Angiotensin II has many direct effects on blood pressure. Erythropoietin stimulates red blood cell production in the bone marrow.

TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108) can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of the kidney. These include, but are not limited to, diseases that affect the four basic morphologic components, glomeruli, tubules, interstitium, and blood vessels. Diseases include, e.g., acute nephritic syndrome, nephritic syndrome, renal failure, urinary tract infections, renal stones, cystic diseases of the kidney, e.g., cystic renal dysplasia, polycystic disease (autosomal dominant and recessive types), medullary cystic disease, acquired cystic disease, renal cysts, parenchymal cysts, perihilar renal cysts (pyelocalyceal cysts, hilar lymphangitic cysts), glomerular diseases, diseases of tubules, tubulointerstitial diseases, tumors of the kidney, such as benign tumors (cortical adenoma, renal fibroma, renomedullary interstitial cell tumor), malignant tumors (renal cell carcinoma, hypernephroma,

adenocarcinoma of kidney, Wilms' tumor, nephroblastoma, urothelial carcinoma), renal coloboma, nephorblastoma, clear cell sarcoma of kidney (CCSK), rhabdoid tumor of kidney (RTK), von Hippel-Lindau disease, oncocytoid renal cell carcinoma (RCC), renal leiomyoblastoma, etc. TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108) can also be used for staging and classifying conditions and diseases of the present invention, alone, or in combination with conventional staging and classification schemes.

Pancreatic Gene Complex

The present invention relates to a cluster of olfactory GPCR (G-protein coupled) receptor genes located at chromosomal band 11q24. These genes are expressed predominantly in pancreatic tissue, establishing this region of chromosome 11 as a unique gene complex involved in pancreatic function. See, Table 12. Because of their exquisite selectivity for pancreatic tissues, the pancreatic gene complex ("PGC"), and the genes which comprise it, are useful to assess pancreas tissue and function for diagnostic, prognostic, therapeutic, and research purposes.

The spatial organization of the pancreatic gene complex ("PGC") is illustrated in Fig. 7. It spans several hundred kilobases of chromosome 11, e.g., from about LOC160205 to LOC119954, from about LOC119944-LOC119954, and any part thereof. Within this region, is a cluster of genes coding for polypeptides which share sequence identity with the olfactory GPCR family. These include, but are not limited to, TMD0986, XM_061780 (TMD0987), XM_061781 (TMD0353), XM_061784 (TMD0989), XM_061785 (TMD058). Fig. 8 illustrates the relationship between the lengths of the different coding sequences. As shown in the figure, XM_061784 is shorter at its C-terminus than the other family members.

As members of the GPCR family, the PGC genes all share a degree of amino acid sequence identity and similarity. See, Table 14 for values (% sequence identity is the first place; % sequence similarity is in parenthesis in the second place; calculations were performed using the publicly-available BLASTP pair-wise alignment program). TMD0986, XM_061780, XM_061781, and XM_061785 each share about 40% sequence identity.

BLAST searching of publicly available sequences indicates that these polypeptides share less amino acid sequence identity with each other than they do with other olfactory GPCR homologs located elsewhere in the genome. Significantly higher amino acid sequence identity – 81% – is observed between the adjacent genes XM_061784 and XM_061785. These genes appear to be part of a sub-cluster within PGC that share high polypeptide similarity between them.

The phrase "a gene of Table 12" which is used throughout the description include the specific sequences for the listed XM numbers as well as other human alleles, and mammalian homologs, such as murine homologs. For example, Table 14 lists several of the mouse homologs that are included in the present invention. While SEQ ID NOS. 152, 153, 162, 163, 167, 168, 171, 172, 175, and 176 may represent particular alleles, the present invention relates to other alleles, as well, including naturally-occurring polymorphisms (i.e., a polymorphism in a nucleotide sequence which is identified in populations of mammals).

TMD0986 (SEQ ID NO 152 and 153) is a full-length sequence of the previously identified XM_061779. It contains an additional 117 amino acids not present in XM_061779. The present invention relates to nucleic acids comprising or consisting essentially of this sequence in its entirety (e.g., amino acids 1-314), comprising or consisting essentially of nucleic acids coding for amino acids 1-117, and comprising or consisting essentially of fragments of nucleic acids coding for amino acids 1-117. Polypeptides encoded by these nucleic acids are also claimed, including polypeptide fragments of 1-117, such as 1-23, 79-97, 164-198, 261-274, and other extracellularly exposed peptides. In addition, the present invention relates to binding partners, such as antibodies, that bind to epitopes within amino acids 1-117 (e.g., SEQ ID NO 153).

Pancreas

Diabetes and other pancreatic disorders are a major health concern. Worldwide, it is estimated that 5-10% of the population suffers from some form of diabetes. Pancreatic cancer is the fifth leading cause of cancer-related mortality. In 2002, it was estimated that about 30,000 Americans would be diagnosed with pancreatic cancer, and 90% would die within 12 months. Despite the prevalence of pancreatic disease, the genetics and physiology of normal pancreatic function and pancreatic disease is still poorly understood.

The pancreas is a mixed gland comprised of exocrine and endocrine tissues. The exocrine portion comprises about 80-85% of the organ. It is divided into lobes by connective tissue septa, and each lobe is divided into several lobules. These lobules are composed of grape-like clusters of secretory cells that form sacs known as acini. An acinus is a functional unit of the pancreatic exocrine gland. All acini drain into interlobular ducts which merge to form the main pancreatic duct. It, in turn, joins together with the bile duct from the liver to form the common bile duct that empties into the duodenum. Pancreatic acinar cells make up more than 80% of the total volume of the pancreas and function in the secretion of the various enzymes that assist digestion in the gastrointestinal tract. Scattered among the acinar cells are approximately a million pancreatic islets ("islets of Langerhans") that secrete the pancreatic endocrine hormones. These dispersed islets comprise approximately 2% of the total volume of the pancreas.

The basic function of the pancreatic endocrine cells is to secrete certain hormones that participate in the metabolism of proteins, carbohydrates, and fats. The hormones secreted by the islets include, e.g., insulin, glucagon, somatostatin, pancreatic polypeptide, amylin, adrenomedullin, gastrin, secretin, and peptide-YY. See, also, Shimizu et al., *Endocrin.*, 139:389-396, 1998. The islets contain about four major and two minor cell types. The major cell types are alpha (glucagon producing), beta (insulin and amylin producing), delta (somatostatin producing which suppresses both insulin and glucagon release), and F (pancreatic polypeptide and adrenomedullin producing) cells. The minor cell types are D1 (produce vasoactive intestinal peptide or VIP) and enterochromaffin (produce serotonin) cells. The cells can be distinguished, e.g., by their morphology, hormonal content, and polynucleotide expression patterns.

The ability of the pancreas to respond to a wide variety of metabolic signals is conferred by an expression profile comprising a rich assortment of receptor proteins. G-protein coupled receptors have been previously identified in the pancreas, including, e.g., receptors for glucagon, secretin, CCK (e.g., Roettger et al., *J. Cell Biol.*, 130:579-590, 1995), purines (e.g., P2 purinoreceptors), gastrin, KiSS-1 peptides (e.g., Kotani et al., *J. Biol. Chem.*, 276:34631-6, 2001), adrenomedullin (Martinez et al., *Endocrin.*, 141:406, 2000), and interleukins. G-protein subunits have also been localized to the pancreas, including G-proteins which were previously associated with the olfactory epithelium. See, e.g., Zigman et

al., *Endocrin.*, 133:2508-2514, 1993. In addition, pancreatic cells express neurotropin, neurotensin, and interleukin receptors.

As mentioned, the pancreas is sensitive to a variety of metabolic, soluble and hormonal signals involved in regulating blood sugar, modulating synthesis and release of pancreatic digestive enzymes, and other physiologically important processes involved in pancreas function. In analogy to the ability of olfactory receptors to detect odors and pheromones in the environment, the pancreatic GPCRs of the present invention can be used to "sniff" out and respond to various ligands in the blood which pass through the pancreas, including peptides, metabolites, and other biologically-active molecules. Biological activities include, but are not limited to, e.g., regulation of blood sugar, modulation of all aspects of the various secreted polypeptides (hormones, enzymes, etc.) produced by the pancreas, ligand-binding, exocytosis, amylase (and any of the other 20 or so digestive enzymes produced by the pancreas) secretion, autocrine responses, apoptosis (e.g., in the survival of beta-islet cells), zymogen granule processing, G-protein coupling activity, etc.

The polynucleotides, polypeptides, and ligands thereto, of the present invention can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of pancreas. These include, but are not limited to, e.g., disorders associated with loss or mutation to 11q24, such as Jacobsen syndrome (OMIM #147791), cystic fibrosis, acute and chronic pancreatitis, pancreatic abscess, pancreatic pseudocyst, nonalcoholic pancreatitis, alcoholic pancreatitis, classic acute hemorrhagic pancreatitis, chronic calcifying pancreatitis, familial hereditary pancreatitis, carcinomas of the pancreas, primary (idiopathic) diabetes (e.g., Type I (insulin dependent diabetes mellitus, IDDM) [insulin deficiency, beta cell depletion], Type II (non-insulin dependent diabetes mellitus, NIDDM) [insulin resistance, relative insulin deficiency, mild beta cell depletion]), nonobese NIDDM, obese NIDDM, maturity-onset diabetes of the young (MODY), islet cell tumors, diffuse hyperplasia of the islets of Langerhans, benign adenomas, malignant islet tumors, hyperfunction of the islets of Langerhans, hyperinsulinism and hypoglycemia, Zollinger-Ellison syndrome, beta cell tumors (insulinoma), alpha cell tumors (glucagonoma), delta cell tumors (somatostatinoma), vipoma (diarrheogenic islet cell tumor), pancreatic cancers, pancreatic carcinoid tumors, multihormonal tumors, multiple endocrine neoplasia (MEN), MEN I (Wermer syndrome), MEN II (Sipple syndrome), MEN III or IIb, pancreatic endocrine

tumors, etc.

In view of its selectivity and display on the cell surface, the olfactory GPCR family members of the present invention are useful targets for histological, diagnostic, and therapeutic applications relating to the cells (e.g., pancreatic progenitor, exocrine, endocrine, acinar, islet, alpha, beta, delta, F, D1, enterochromaffin, etc.) in which they are expressed. Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging, therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such as antibodies, can be used to treat carcinomas in analogy to how c-erbB-2 antibodies are used to breast cancer. They can also be used to detect metastatic cells, in biopsies to identify bone marrow, lymphocytes, etc. The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or other binding partners include those that are specific for parts of the polypeptide which are exposed extracellularly as indicated in Table 14. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold, etc., or more) in that tissue when compared to other tissue-types.

The present invention relates to methods of detecting pancreas cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for a gene of Table 12, or a mammalian homolog thereof, under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization. Detecting can be accomplished by any suitable method and

technology, including, e.g., any of those mentioned and discussed below, such as Northern blot and PCR. Specific polynucleotides include SEQ ID NOS 154, 155, 164, 165, 169, 170, 173, 174, 177, and 178, and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g., monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting a pancreas cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by a polypeptide of Table 12, or a mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding assays can be accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface as indicated in Table 14.

As indicated above, binding partners can be used to deliver agents specifically to the pancreas, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of delivering an agent to a pancreas cell can comprise, e.g., contacting a pancreas cell with an agent coupled to a binding partner specific for a polypeptide coding for a gene of Table 12, whereby said agent is delivered to said cell. Any type of agent can be used, including, therapeutic and imaging agents. Contact with the pancreas can be achieved in any effective manner, including by administering effective amounts of the agent to a host orally, parentally, locally, systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent is associated with the binding partner in such a manner that it can be carried specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target), present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers. Any cell expressing a polypeptide coded for by a gene of Table 12 can be targeted, including, e.g., pancreatic progenitor, exocrine, endocrine, secretory, acinar, islet, alpha, beta, delta, F, D1, enterochromaffin, etc.

Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body.

Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintographic. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos, 6,264,917, 6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The methods described therein can be used generally to associate a partner with an agent for any desired purpose. See, Bruehlmeier et al., *Nucl. Med. Biol.*, 29:321-327, 2002, for imaging pancreas using labeled receptor ligands. Antibodies and other ligands to receptors of the present invention can be used analogously.

A pancreas cell (see above for examples of pancreas cell types) can also be modulated in accordance with the present invention, e.g., by methods of modulating a pancreas cell, comprising, e.g., contacting said cell with an agent effective to modulate a gene of Table 12, or the biological activity of a polypeptide encoded thereby (e.g., SEQ ID NO 153, 163, 168, 172, or 176), or a mammalian homolog thereof, whereby said pancreas cell is modulated. Modulation as used throughout includes, e.g., stimulating, increasing, agonizing, activating, amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.

An activity or function of the pancreas cell can be modulated, including, e.g., regulation of blood sugar, modulation of all aspects of the various secreted polypeptides (hormones, enzymes, etc.) produced by the pancreas, ligand-binding, exocytosis, amylase (and any of the other 20 or so digestive enzymes produced by the pancreas) secretion, autocrine responses, apoptosis (e.g., in the survival of beta-islet cells), etc.

The present invention also relates to polypeptide detection methods for assessing pancreas function, e.g., methods of assessing pancreas function, comprising, detecting a polypeptide coded for by a gene of Table 12, fragments thereof, polymorphisms thereof, in a body fluid, whereby the level of said polypeptide in said fluid is a measure of pancreas function. Pancreas function tests are usually performed to determine whether the pancreas is functioning normally as a way of diagnosing pancreas disease. Various tests are commonly used, including, e.g., assays for the presence of pancreatic enzymes in body fluids (e.g.,

amylase, serum lipase, serum trypsin-like immuoreactivity), studies of pancreatic structure (e.g., using x-ray, sonography, CT-scan, angiography, endoscopic retrograde cholangiopancreatography), and tests for pancreatic function (e.g., secretin-pancreozymin (CCK) tst, Lundh meal test, Bz-Ty-PABA test, chymotrypsin in feces, etc). Detection of a polypeptide coded for by a gene of Table 12 provides an additional assessment tool, especially in diseases such as pancreatitis and pancreatic cancer where pancreatic markers can appear in the blood, stool, urine, and other body fluids. As with the other tests, elevated levels of said polypeptide in blood, or other fluids, can indicate impaired pancreas function. Values can be determined routinely, as they are for other markers , such as those mentioned above. Detecting can be performed routinely (see below), e.g., using an antibody which is specific for said polypeptide, by RIA, ELISA, or Western blot, etc., in analogy to the tests for pancreatic enzymes in body fluids.

Promoter sequences obtained from GPCR genes of the present invention can be utilized to selectively express heterologous genes in pancreas cells. Methods of expressing a heterologous polynucleotide in pancreas cells can comprise, e.g., expressing a nucleic acid construct in pancreas cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected SEQ ID NOS 156-161, 166, 179, or 180. In addition to the cell lines mentioned below, the construct can be expressed in primary cells or in established cell lines.

The genes and polypeptides of Table 12 can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of the pancreas as mentioned above. The present invention relates to methods of identifying a pancreatic disease or pancreatic disease-susceptibility, comprising, e.g., determining the association of a pancreatic disease or pancreatic disease-susceptibility with a nucleotide sequence present within the pancreatic gene complex. An association between a pancreas disease or disease-susceptibility and nucleotide sequence includes, e.g., establishing (or finding) a correlation (or relationship) between a DNA marker (e.g., gene, VNTR, polymorphism, EST, etc.) and a particular disease state. Once a relationship is identified, the DNA marker can be utilized in diagnostic tests and as a drug target.

Any region of the pancreatic gene complex can be used as a source of the DNA marker (e.g., a nucleotide sequence present with PGC), including, e.g., TMD0986,

XM_061780 (TMD0987), XM_061781 (TMD0353), XM_061784 (TMD0989), XM_061785 (TMD058), and any part thereof, introns, intergenic regions, any DNA from about 29160-29310 kb of 11q24, NT_009215, etc.

Human linkage maps can be constructed to establish a relationship between a region within 11q24 and a pancreatic disease or condition. Typically, polymorphic molecular markers (e.g., STRP's, SNP's, RFLP's, VNTR's) are identified within the region, linkage and map distance between the markers is then established, and then linkage is established between phenotype and the various individual molecular markers. Maps can be produced individual family, selected populations, patient populations, etc. In general, these methods involve identifying a marker associated with the disease (e.g., identifying a polymorphism in a family which is linked to the disease) and then analyzing the surrounding DNA to identity the gene responsible for the phenotype.

Retina Selective Gene

The present invention relates to NM_013941 (GPCR181 or OR10C1), a multiple transmembrane spanning polypeptide which shares sequence identity with the olfactory G-protein coupled receptor (GPCR) family. Like other GPCR, NM_013941 has seven transmembrane domains, at about amino acid positions 20-42, 54-76, 91-113, 134-156, 190-212, 233-255, and 265-287, of SEQ ID NO 182. It is located at about chromosomal band 6p21.31-22.2. There are several other GPCRs located nearby (e.g., OR2B3, AL022727; OR2J3, AL022727). NM_013941 is highly expressed in brain tissue, at lower levels in heart, pituitary, and skin, and at minimally detectable levels in colon, small intestine, kidney, lymphocytes, and mammary gland. In the neuronal tissue, it was selectively expressed in the retina, but was not detected in any other brain tissue regions. The selective expression of NM_013941 in the retina makes it useful as a marker for retinal tissue, e.g., in stem cell cultures and biopsy samples, as well as a diagnostic, prognostic, therapeutic, and research tool for any conditions, diseases, disorders, or applications associated with the retina and the cells in which it is expressed. NM_013941 includes both human and mammalian homologs of it (e.g., mouse XM_111729 which is similar to olfactory receptor MOR263-6). SEQ ID NOS. 181 and 182 represent a particular allele of NM_013941; the present invention relates to other alleles, as well, including naturally-occurring polymorphisms (i.e., a polymorphism in the nucleotide sequence which is identified in populations of mammals).

The chromosomal region within which NM_013941 is located comprises a number of genes involved in retinal function. These include, e.g., retinal cone dystrophy (OMIM 602093) which appears to be a result of mutation in guanylate cyclase activator-1A (e.g., Payne et al., *Human Molec. Genet.*, 7:273-277, 1998), retinal degeneration slow (OMIM 179605) which appears to be a defect in specific retinal protein homologous to rod outer segment protein-1, retinitis pigmentosa-7, retinitis pigmentosa-14 (OMIM 600132) which is associated with a mutation in the tubby-like protein TULP1 (e.g., Banerjee et al., *Nature Genet.*, 18:177-179, 1998; Hagstrom et al., *Nature Genet.*, 18:174-176, 1998), and others. Thus, this region appears to be important in eye function.

In view of its selectivity and display on the cell surface, the olfactory GPCR family members of the present invention are useful targets for histological, diagnostic, and therapeutic applications relating to retinal cells. Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging, therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such as antibodies, can be used to treat retinal carcinomas (e.g., retinoblastoma) in analogy to how c-erbB-2 antibodies are used to breast cancer. See, e.g., Hayashi et al., *Invest. Ophthalmol. Vis. Sci.*, 40:265-72, 1999 for an example treating retinoblastoma using HSV-TK. Transfer of the gene into the retinal cells can be achieved by incorporating the gene into liposomes which have been made cell-selective by incorporating a NM_013941 specific antibody into its bilayer. See, also, Wu and Wu, *J. Biol. Chem.*, 262: 4429-4432, 1987.

The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or other binding partners include those that are specific for parts of the polypeptide which are exposed extracellularly. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule

comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold, etc., or more) in that tissue when compared to other tissue-types.

The present invention relates to methods of detecting retinal cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for NM_013941 (e.g., SEQ ID NOS 181), or a mammalian homolog thereof, under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization. Detecting can be accomplished by any suitable method and technology, including, e.g., any of those mentioned and discussed below, such as Northern blot and PCR. Specific polynucleotides include SEQ ID NOS 183 and 184, and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g., monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting a retinal cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by NM_013941 (e.g., SEQ ID NO 182), or a mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding assays can be accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface.

As indicated above, binding partners can be used to deliver agents specifically to the retina, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of delivering an agent to a retinal cell can comprise, e.g., contacting a retinal cell with an agent coupled to binding partner specific for NM_013941 (SEQ ID NO 182), whereby said agent is delivered to said cell. Any type of agent can be used, including, therapeutic and imaging agents. Contact with the retinal can be achieved in any effective manner, including by administering effective amounts of the agent to a host orally, parentally, locally, systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent

is associated with the binding partner in such a manner that it can be carried specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target), present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers. Any cell expressing a polypeptide coded for by NM_013941 can be targeted, including, e.g., pigmented epithelial cells, photoreceptor cells, cones, rods, bipolar cells, ganglion cells, etc.

Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body. Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintographic. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos, 6,264,917, 6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The methods described therein can be used generally to associate a partner with an agent for any desired purpose.

A retinal cell (see above for examples of retinal cell types) can also be modulated in accordance with the present invention, e.g., by methods of modulating a retinal cell, comprising, e.g., contacting said cell with an agent effective to modulate NM_013941, or the biological activity of a polypeptide encoded thereby (e.g., SEQ ID NO 182), or a mammalian homolog thereof, whereby said retinal cell is modulated. Modulation as used throughout includes, e.g., stimulating, increasing, agonizing, activating, amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.

Any activity or function of the retinal cell can be modulated, including, e.g., light reception, phototransduction, excitation of rods, excitation of cones, metabolism of vitamin A, retinal, rhodopsin, and other functional molecules, cGMP binding and hydrolysis, sodium channel flux, membrane potential, phosphodiesterase activity, G-protein activity and coupling, vitamin A processing, sodium pump activity, calcium flux, etc. The response of a retinal cell to stimuli can also be modulated, including, but not limited to, ligands to

NM_013941, light, ion levels, second messenger levels, etc.

Promoter sequences can be utilized to selectively express heterologous genes in retinal cells. Methods of expressing a heterologous polynucleotide in retinal cells can comprise, e.g., expressing a nucleic acid construct in retinal cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is obtained from NM_01394, e.g., on genomic NT_007592. In addition to the cell lines mentioned below, the construct can be expressed in primary cells or in established cell lines.

Retina

The retina is a two-layered structure located on the back of the eye. It is the primary organ responsible for vision. The outer pigmented layer is comprised of pigmented epithelial cells that absorb light, preventing it from scattering in the eye, and store vitamin A needed by the photoreceptor cells. The inner neural layer is comprised of three main cell types: photoreceptor cells, bipolar cells, and ganglion cells. The local currents generated by a light stimulus spreads from the photoreceptor cells to the bipolar cells, and then on to the innermost ganglion cells. The optic disc is the exit site of the retinal ganglion axons which then bundle into the optic nerve

Photoreceptors consist of rods and cones which are the photosensitive cells of the retina. Each rod and cone elaborates a specialized cilium, called the outer segment, that contains the phototransduction machinery. The rods contain a specific light-absorbing visual pigment, rhodopsin. In humans, there are three classes of cones, each characterized by the expression of distinct visual pigments: the blue cone, green cone and red cone pigments. Each type of visual pigment protein is tuned to absorb light maximally at different wavelengths. The rod rhodopsin mediates scotopic vision (in dim light), whereas the cone pigments are responsible for photopic vision (in bright light). The red, blue and green pigments also form the basis of color vision.

NM_013941 can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of the retinal. These include, but are not limited to, diseases that affect the basic morphologic components as mentioned above, e.g., the outer and inner cell layers, and the optic nerve the retina. Diseases include, e.g.,

retinal degeneration, retinal degenerations such as retinitis pigmentosa, Bardet-Biedl syndrome, Bassen-Kornzweig syndrome (abetalipoproteinemia), Best disease (vitelliform dystrophy), choroidemia, gyrate atrophy, congenital amaurosis, Refsum syndrome, Stargardt disease, Usher syndrome, macular degeneration (dry and wet forms), diabetic retinopathy, peripheral vitreoretinopathies, photic retinopathies, surgery-induced retinopathies, viral retinopathies (such as HIV retinopathy related to AIDS), ischemic retinopathies, retinal detachment, traumatic retinopathy, optic neuropathy, optic neuritis, ischemic optic neuropathy, Leber optic neuropathy, diseases of Bruch's membrane, glaucoma, cancer, retinoblastoma, cancer- associated retinopathy syndrome (CAR syndrome), melanoma-associated retinopathy (MAR), etc. NM_013941 can also be used for staging and classifying conditions and diseases of the present invention, alone, or in combination with conventional staging and classification schemes.

Spleen Gene Cluster

The present invention relates to a cluster of transmembrane and GPCR-type receptor genes located at chromosomal band 11q12.2. The genes of the present invention are expressed predominantly in the spleen (e.g., Fig. 10, lane 19) (hence, "spleen gene" cluster), as well as other tissues of the immune and reticuloendothelial system (RES), establishing this region of the chromosome as a unique gene complex involved in spleen, lymphoid, and/or reticuloendothelial function. TMD1030 and TMD0621 are highly expressed in spleen tissue, with insignificant levels in other tissues. In addition to spleen. TMD1029 and TMD1029 show significant expression in the liver and lymphocytes, as well. Because of their selectivity for spleen, lymphoid, and/or reticuloendothelial tissues, the gene complex, and the chromosomal region which comprises it, are useful to assess spleen, lymphoid, and/or reticuloendothelial tissue function and for diagnostic, prognostic, therapeutic, and research purposes. Information on the genes is summarized in Tables 15-19.

The spatial organization of the gene complex is illustrated in Fig. 11. The complex spans about at least 100 kb, from about EST markers G62658, SHGC-82134, etc. (located at the end closest to the centromere and TMD1030) to SHGC-154002, SHGC-9433, etc. (located at the end furthest from the centromere and TMD0621). All the genes have the same orientation of transcription. TMD1799 (XM_166849) (SEQ ID NO 193-194), located at the

upper region, shows very high expression in lymphocytes, but only marginal expression in spleen, indicating that expression in lymphocytes may predominate at the boundaries of the gene complex. In the lower region, TMD1027 (XM_166856) (SEQ ID NO 195-196), spleen expression virtually disappears, while lymph node expression becomes very high. The present invention includes this entire region, and any parts thereof. For instance, the present invention includes any DNA fragments within it which confer the observed tissue specificities described herein.

The gene complex is involved in spleen, immune, and RES functions. The spleen is located in the left upper region of the abdomen. In the adult, it weights about 90-180 grams, and is about 1[illegible] by 7.5 cm in size. The spleen is anatomically and functionally compartmentalized into two distinct regions, the red and white pulp. The red pulp comprises blood vessels interwoven with connective tissue ("pulp cords") that is lined with reticuloendothelial cells. It possesses a blood filtering function, removing opsonized cells and trapping abnormal red blood cells. It also is a storage reservoir for platelets and other blood cells. In the fetus, the red pulp has a hematopoietic function. Inside the red pulp, is lymphoid tissue know as the white pulp. Antibodies are made inside the white pulp. Similar to other lymphatic tissues, B- and T-cell's mature inside the white pulp, where they are involved in antigen presentation and lymphocyte maturation. The white pulp is clustered around the periarteriolar lymphoid sheath, and is comprised of follicles and marginal zone. Naive B-cells are located in the primary follicle, memory cells, macrophages, and dendritic cells in the secondary follicle, and macrophages and B-cells in the marginal zone. The integrins LFA-1 and alpha4-beta1 are involved in localization of the B-cells to the marginal zone of the white pulp (Lu and Cyster, *Science*, 297:409, 2002).

The reticuloendothelial system (RES) is a multi-organ phagocytic system involved in removing particulates from the blood. It is comprised of the spleen and liver. It has the ability to sequester inert particles and dyes. Cells of the RES system include, macrophages, liver Kuppfer cells, endothelial cells lining the sinusoids of the liver, spleen, and bone marrow, and reticular cells of lymphatic and bone marrow tissues.

The polynucleotides, polypeptides, and ligands thereto, of the present invention can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of spleen, lymphoid, and/or reticuloendothelial tissues. These include, but are not limited to, splenomegaly, hypersplenism, hemolytic anemis, hereditary

spherocytosis, hereditary eliptocytosis, thalassemia minor and major, autoimmune hemolytic anemia, thrombocytopenia, idiopathic thrombocytopenic purpura, immunologic thrombocytopenia associated with chronic lymphocytic leukemia or systemic lupus erythematosis, TTP, leukemia, lymphoma, primary and metastatic tumors, splenic cysts, infection, inflammatory diseases, anemias, blood cancers, etc. See, Table 19 for other examples.

In view of their selectivity and display on the cell surface, the genes of the present invention are useful targets for histological, diagnostic, and therapeutic applications relating to the cells (e.g., reticuloendothelial cells, macrophages, Kupffer cells, monocytes, B-lymphocytes, T-lymphocytes, etc) in which they are expressed. Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging, therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such as antibodies, can be used to treat carcinomas in analogy to how c-erbB-2 antibodies are used to treat breast cancer. They can also be used to detect metastatic cells in biopsies. The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or other binding partners include those that are specific for parts of the polypeptide which are exposed extracellularly. See, Table 16. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold, etc., or more) in that tissue when compared to other tissue-types. TMD1030 and TMD0621 are predominantly and selectively expressed in spleen tissue.

The expression patterns of the selectively expressed polynucleotides disclosed herein can be described as a "fingerprint" in that they are a distinctive pattern displayed by a tissue. Just as with a fingerprint, an expression pattern can be used as a unique identifier to characterize the status of a tissue sample. The list of expressed sequences disclosed herein provides an example of such a tissue expression profile. It can be used as a point of reference to compare and characterize samples. Tissue fingerprints can be used in many ways, e.g., to classify an unknown tissue, to determine the origin of metastatic cells, to assess the physiological status of a tissue, to determine the effect of a particular treatment regime on a tissue, to evaluate the toxicity of a compound on a tissue of interest, etc.

For example, the tissue-selective polynucleotides disclosed herein represent the configuration of genes expressed by a normal tissue. To determine the effect of a toxin on a tissue, a sample of tissue can be obtained prior to toxin exposure ("control") and then at one or more time points after toxin exposure ("experimental"). An array of tissue-selective probes can be used to assess the expression patterns for both the control and experimental samples. As discussed in more detail below, any suitable method can be used. For instance, a DNA microarray can be prepared having a set of tissue-selective genes arranged on to a small surface area in fixed and addressable positions. RNA isolated from samples can be labeled using reverse transcriptase and radioactive nucleotides, hybridized to the array, and then expression levels determined using a detection system. Several kinds of information can be extracted: presence or absence of expression, and the corresponding expression levels. The normal tissue would be expected to express substantially all the genes represented by the tissue-selective probes. The various experimental conditions can be compared to it to determine whether a gene is expressed, and how its levels match up to the normal control.

While the expression profile of the complete gene set represented by the sequences disclosed here may be most informative, a fingerprint containing expression information from less than the full collection can be useful, as well. In the same way that an incomplete fingerprint may contain enough of the pattern of whorls, arches, loops, and ridges, to identify the individual, a cell expression fingerprint containing less than the full complement may be adequate to provide useful and unique identifying and other information about the sample. Moreover, because of heterogeneity of the population, as well differences in the particular physiological state of the tissue, a tissue's "normal" expression profile is expected to differ

between samples, albeit in ways that do not change the overall expression pattern. As a result of these individual differences, each gene although expressed selectively in spleen, may not on its own 100% of the time be adequately enough expressed to distinguish said tissue. Thus, the genes can be used in any of the methods and processes mentioned above and below as a group, or one at a time.

The present invention relates to methods of detecting spleen, lymphoid, and/or reticuloendothelial cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), or a mammalian homolog thereof, under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization. Detecting can be accomplished by any suitable method and technology, including, e.g., any of those mentioned and discussed below, such as Northern blot and PCR. Specific polynucleotides include SEQ ID NOS 197-204 listed in Table 17, and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g., monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting a spleen, lymphoid, and/or reticuloendothelial cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by a polypeptide of the present invention, or a mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding assays can be accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface. Detection can be useful for assessing spleen integrity, e.g., when it is suspected that the spleen is damaged and undergoing deterioration. The appearance of polypeptides of the present invention in body fluids, such as blood, can indicate spleen damage, including neoplastic and/or apoptotic changes.

As indicated above, binding partners can be used to deliver agents specifically to the spleen, lymphoid, and/or reticuloendothelial tissues, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of delivering an agent to a spleen, lymphoid, and/or

reticuloendothelial cell can comprise, e.g., contacting a spleen, lymphoid, and/or reticuloendothelial cell with an agent coupled to a binding partner specific for a polypeptide coding for TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), whereby said agent is delivered to said cell. Any type of agent can be used, including, therapeutic and imaging agents. Contact with the spleen, lymphoid, and/or reticuloendothelial tissue can be achieved in any effective manner, including by administering effective amounts of the agent to a host orally, parenterally, locally, systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent is associated with the binding partner in such a manner that it can be carried specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target), present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers. Any cell expressing a polypeptide coded for by TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205) can be targeted, including, e.g., reticuloendothelial cells, macrophages, Kupffer cells, lymphocytes, B-lymphocytes, T-lymphocytes, etc.

Antibodies (alone or conjugated to active agents) can be used to ablate spleen and other tissues. For instance, in diseases where splenectomy is indicated (e.g., immune thrombocytopenic purpura, autoimmune hemolytic anemia, blood cell disorders, myeloproliferative disorders, tumors, hypersplenism, etc.), antibodies to TMD1030 and TMD0621 can be used to ablate spleen tissue, or block spleen function.

Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body. Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintiographic imaging. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos, 6,264,917, 6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The

methods described therein can be used generally to associate a partner with an agent for any desired purpose. See, Bruehlmeier et al., *Nucl. Med. Biol.*, 29:321-327, 2002, for imaging using labeled receptor ligands. Antibodies and other ligands to receptors of the present invention can be used analogously.

A cell (see above for examples of spleen, lymphoid, and/or reticuloendothelial cell types) can also be modulated in accordance with the present invention, e.g., by methods of modulating a spleen, lymphoid, and/or reticuloendothelial cell, comprising, e.g., contacting said cell with an agent effective to modulate TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), or the biological activity of a polypeptide encoded thereby (e.g., SEQ ID NOS 185-192), or a mammalian homolog thereof, whereby said spleen, lymphoid, and/or reticuloendothelial cell is modulated. Modulation as used throughout includes, e.g., stimulating, increasing, agonizing, activating, amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.

Any activity or function of the spleen, lymphoid, and/or reticuloendothelial tissues can be modulated, including, e.g., immune modulation (e.g., modulating antigen presentation, antibody production and secretion, humoral and cellular responses, etc.), sequestration and removal of red blood cells, clearance of microorganisms and particular antigens from blood, migration into the marginal zone or other immune and RES compartments, etc.

The present invention also relates to polypeptide detection methods for assessing spleen, lymphoid, and/or reticuloendothelial tissue function, e.g., methods of assessing spleen, lymphoid, and/or reticuloendothelial function, comprising, detecting a polypeptide coded for by TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), fragments thereof, polymorphisms thereof, in a body fluid, whereby the level of said polypeptide ~~in said fluid~~ is a ~~measure of spleen~~, lymphoid, and/~~or~~ reticuloendothelial function. spleen, lymphoid, and/or reticuloendothelial function tests are usually performed to determine whether the spleen, lymphoid, and/or reticuloendothelial tissue is functioning normally as a way of diagnosing spleen, lymphoid, and/or reticuloendothelial disease. Various tests are commonly used, including, e.g., 99Tc-colloid liver-spleen scan, computed tomography, ultrasound scanning of left upper quandrant, MRI, liver enzymes, etc.

Detection of a polypeptide coded for by TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), provides an additional assessment tool, especially in diseases or disorders, such as splenomegaly, hypersplenism, or ruptured spleen, where said polypeptides can appear in the blood, stool, urine, and other body fluids. As with the other tests, elevated levels of said polypeptide in blood, or other fluids, can indicate impaired spleen, lymphoid, and/or reticuloendothelial function. Values can be determined routinely, as they are for other markers , such as those mentioned above. Detecting can be performed routinely (see below), e.g., using an antibody which is specific for said polypeptide, by RIA, ELISA, or Western blot, etc., in analogy to the tests for enzymes and other proteins in body fluids.

Promoter sequences obtained from genes of the present invention can be utilized to selectively express heterologous genes in cells. Methods of expressing a heterologous polynucleotide in cells, e.g., spleen, lymphoid, and/or reticuloendothelial cells can comprise, e.g., expressing a nucleic acid construct in spleen, lymphoid, and/or reticuloendothelial cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected SEQ ID NOS 205-213. In addition to the cell lines mentioned below, the construct can be expressed in primary cells or in established cell lines.

The genes and polypeptides of the present invention can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of the spleen, lymphoid, and/or reticuloendothelial tissues mentioned above. The present invention relates to methods of identifying a genetic basis for a disease or disease-susceptibility, comprising, e.g., determining the association of a spleen, lymphoid, and/or reticuloendothelial disease or spleen, lymphoid, and/or reticuloendothelial disease-susceptibility with the gene complex of the present invention, e.g., a nucleotide sequence present in the gene complex at 11q12.2. An association between a spleen, lymphoid, and/or reticuloendothelial disease or disease-susceptibility and nucleotide sequence includes, e.g., establishing (or finding) a correlation (or relationship) between a DNA marker (e.g., gene, VNTR, polymorphism, EST, etc.) and a particular disease state. Once a relationship is identified, the DNA marker can be utilized in diagnostic tests and as a drug target.

Any region of the gene can be used as a source of the DNA marker, exons, introns,

intergenic regions, or any DNA from the gene cluster of the present invention at chromosomal region 11q12.2, etc.

Human linkage maps can be constructed to establish a relationship between a gene and a spleen, lymphoid, and/or reticuloendothelial disease or condition. Typically, polymorphic molecular markers (e.g., STRP's, SNP's, RFLP's, VNTR's) are identified within the region, linkage and map distance between the markers is then established, and then linkage is established between phenotype and the various individual molecular markers. Maps can be produced for an individual family, selected populations, patient populations, etc. In general, these methods involve identifying a marker associated with the disease (e.g., identifying a polymorphism in a family which is linked to the disease) and then analyzing the surrounding DNA to identity the gene responsible for the phenotype.

The present invention also relates to methods of expressing a polynucleotide in spleen, lymphoid, and/or reticuloendothelial tissue, comprising, e.g., inserting a polynucleotide, which is operably linked to an expression control sequence, into the spleen, lymphoid, and/or reticuloendothelial gene complex at chromosomal location 11q12.2 of a target cell, and growing said cell under conditions effective to express said polynucleotide.

The polynucleotide of interest can be inserted into the target chromosomal region by any suitable method, including, e.g., by gene targeting methods, such as homologous recombination, or by random insertion methods where transformed cells are subsequently screened for insertion into the desired chromosomal site. Chromosome engineering methods are discussed in more detail below, e.g., in the section on transgenic animals. By the phrase "spleen, lymphoid, and/or reticuloendothelial gene complex," it is meant the region of the chromosome in which the cluster of genes, e.g., TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), and TMD0621 (XM_166205), of the present invention are located. Inserting an expressible polynucleotide (e.g., a polynucleotide operably linked to a promoter sequence) into this region confers the tissue expression selectivity which is characteristic of the gene cluster. Any polynucleotide of interest can be inserted into the chromosomal region, including, e.g., polynucleotides encoding polypeptides, antisense polynucleotides, etc.

A cell comprising a polynucleotide inserted into the target chromosomal location can be utilized in vitro or in vivo, e.g., in a transgenic animal. The cell is grown under conditions

which are suitable to achieve polynucleotide expression. These conditions depend upon the cell's environment, e.g., tissue culture cell, or in the form of a transgenic animal.

Pancreas membrane protein genes

The present invention relates to all facets of pancreas membrane protein genes, polypeptides encoded by them, antibodies and specific binding partners thereto, and their applications to research, diagnosis, drug discovery, therapy, clinical medicine, forensic science and medicine, etc. The polynucleotides and polypeptides are useful in variety of ways, including, but not limited to, as molecular markers, as drug targets, and for detecting, diagnosing, staging, monitoring, prognosticating, preventing or treating, determining predisposition to, etc., diseases and conditions, such as pancreatic cancer, diabetes, pancreatitis, and other disorders especially relating to the pancreas and the functions its performs. The identification of specific genes, and groups of genes, expressed in pathways physiologically relevant to pancreas tissue permits the definition of functional and disease pathways, and the delineation of targets in these pathways which are useful in diagnostic, therapeutic, and clinical applications. The present invention also relates to methods of using the polynucleotides and related products (proteins, antibodies, etc.) in business and computer-related methods, e.g., advertising, displaying, offering, selling, etc., such products for sale, commercial use, licensing, etc.

The function, structure, and diseases of the pancreas were described previously. The polynucleotides, polypeptides, and ligands thereto, of the present invention can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of pancreas. These include, but are not limited to, e.g., acute and chronic pancreatitis, pancreatic abscess, pancreatic pseudocyst, nonalcoholic pancreatitis, alcoholic pancreatitis, classic acute hemorrhagic pancreatitis, chronic calcifying pancreatitis, familial hereditary pancreatitis, carcinomas of the pancreas, primary (idiopathic) diabetes (e.g., Type I (insulin dependent diabetes mellitus, IDDM) [insulin deficiency, beta cell depletion], Type II (non-insulin dependent diabetes mellitus, NIDDM) [insulin resistance, relative insulin deficiency, mild beta cell depletion]), nonobese NIDDM, obese NIDDM, maturity-onset diabetes of the young (MODY), islet cell tumors, diffuse hyperplasia of the islets of Langerhans, benign adenomas, malignant islet tumors, hyperfunction of the islets of Langerhans, hyperinsulinism and hypoglycemia, Zollinger-Ellison syndrome, beta cell

tumors (insulinoma), alpha cell tumors (glucagonoma), delta cell tumors (somatostatinoma), vipoma (diarrheogenic islet cell tumor), pancreatic cancers, pancreatic carcinoid tumors, multihormonal tumors, multiple endocrine neoplasia (MEN), MEN I (Wermer syndrome), MEN II (Sipple syndrome), MEN III or IIb, pancreatic endocrine tumors, etc.

For example, five different pancreatic tumor samples were examined (Nos. 1, 2, 3, 4, and 5). TMD0639 was up-regulated in about 1/5 pancreatic cancers (No. 4), TMD0645 was up-regulated in about 3/5 pancreatic cancers (Nos. 2, 3, and 5), and TMD1127 was up-regulated in about 2/5 pancreatic cancers (Nos. 1 and 4). These results indicate that the probes can be used in combination in order to maximize the detection of different types of pancreatic cancers and tumors. Thus, a sample from a patient can be assesses for expression of both TMD0645 and TMD1127 to increase the probability that the pancreas cancer will be detected.

In view of their selectivity and display on the cell surface, the membrane proteins of the present invention are useful targets for histological, diagnostic, and therapeutic applications relating to the cells (e.g., pancreatic progenitor, exocrine, endocrine, acinar, islet, alpha, beta, delta, F, D1, enterochromaffin, etc.) in which they are expressed. Antibodies and other protein binding partners (e.g., ligands, aptamers, small peptides, etc.) can be used to selectively target agents to a tissue for any purpose, included, but not limited to, imaging, therapeutic, diagnostic, drug delivery, gene therapy, etc. For example, binding partners, such as antibodies, can be used to treat carcinomas in analogy to how c-erbB-2 antibodies are used to breast cancer. They can also be used to detect metastatic cells in biopsies and other tissue samples. The genes and polypeptides encoded thereby can also be used in tissue engineering to identify tissues as they appear during the differentiation process, to target tissues, to modulate tissue growth (e.g., from starting stem cell populations), etc. Useful antibodies or other binding partners include those that are specific for parts of the polypeptide which are exposed extracellularly as indicated in Table 21. Any of the methods described above and below can be accomplished in vivo, in vitro, or ex vivo.

When expression is described as being "predominantly" in a given tissue, this indicates that the gene's mRNAs levels are highest in this tissue as compared to the other tissues in which it was measured. Expression can also be "selective," where expression is observed. By the phrase "selectively expressed," it is meant that a nucleic acid molecule

comprising the defined sequence of nucleotides, when produced as a transcript, is characteristic of the tissue or cell-type in which it is made. This can mean that the transcript is expressed only in that tissue and in no other tissue-type, or it can mean that the transcript is expressed preferentially, differentially, and more abundantly (e.g., at least 5-fold, 10-fold, etc., or more) in that tissue when compared to other tissue-types.

Table 20 is a summary of the genes of the present invention which are expressed selectively and/or predominantly in pancreas tissue. Fig. 12 is an illustration of these expression patterns. Each gene is associated with a Clone ID and Accession Number ("ACCN"). The Clone ID is an arbitrary identification number for the clone, and the accession number is the number by which it is listed in GenBank. Although specific sequences are disclosed herein, and listed in GenBank by an accession number), the present invention includes all forms of the gene, including polymorphisms, allelic variations, SNPs, splice variants, and any full-length versions when the disclosed or Genbank version is partial. For convenience, these genes, and their homologs in other species, are referred to throughout the disclosure in shorthand as "the genes of Table 20," "a gene of Table 20," "polynucleotides of Table 20," "polypeptides of Table 20," etc.., because Table 20 contains a listing of the genes by accession number and clone ID.

The expression patterns of the selectively and/or predominantly expressed polynucleotides disclosed herein can be described as a "fingerprint" in that they are a distinctive pattern displayed by pancreas tissue. Just as with a fingerprint, an expression pattern can be used as a unique identifier to characterize the status of a tissue sample. The list of expressed sequences disclosed herein provides an example of such a tissue expression profile. It can be used as a point of reference to compare and characterize samples. Tissue fingerprints can be used in many ways, e.g., to classify an unknown tissue, to determine the origin of metastatic cells, to assess the physiological status of a tissue, to determine the effect of a particular treatment regime on a tissue, to evaluate the toxicity of a compound on a tissue of interest, etc.

For example, the pancreas-selective polynucleotides disclosed herein represent the configuration of genes expressed by a normal pancreas tissue. To determine the effect of a toxin on a tissue, a sample of tissue can be obtained prior to toxin exposure ("control") and then at one or more time points after toxin exposure ("experimental"). An array of pancreas-

selective probes can be used to assess the expression patterns for both the control and experimental samples. As discussed in more detail below, any suitable method can be used. For instance, a DNA microarray can be prepared having a set of pancreas-selective genes arranged on to a small surface area in fixed and addressable positions. RNA isolated from samples can be labeled using reverse transcriptase and radioactive nucleotides, hybridized to the array, and then expression levels determined using a detection system. Several kinds of information can be extracted: presence or absence of expression, and the corresponding expression levels. The normal tissue would be expected to express substantially all the genes represented by the tissue-selective probes. The various experimental conditions can be compared to it to determine whether a gene is expressed, and how its levels match up to the normal control.

While the expression profile of the complete gene set represented by the sequences disclosed here may be most informative, a fingerprint containing expression information from less than the full collection can be useful, as well. In the same way that an incomplete fingerprint may contain enough of the pattern of whorls, arches, loops, and ridges, to identify the individual, a cell expression fingerprint containing less than the full complement may be adequate to provide useful and unique identifying and other information about the sample. Moreover, because of heterogeneity of the population, as well differences in the particular physiological state of the tissue, a tissue's "normal" expression profile is expected to differ between samples, albeit in ways that do not change the overall expression pattern. As a result, a complete match with a particular tissue expression profile, as shown herein, is not necessary.

The present invention relates to methods of detecting pancreas cells, comprising one or more of the following steps, e.g., contacting a sample comprising cells with a polynucleotide specific for a gene of Table 20, or a mammalian homolog thereof, under conditions effective for said polynucleotide to hybridize specifically to said gene, and detecting specific hybridization. Detecting can be accomplished by any suitable method and technology, including, e.g., any of those mentioned and discussed below, such as Northern blot and PCR. Specific polynucleotides include the primer sequences shown in Table 23, and complements thereto.

Detection can also be achieved using binding partners, such as antibodies (e.g.,

monoclonal or polyclonal antibodies) that specifically recognize polypeptides coded for by genes of the present invention. Thus, the present invention relates to methods of detecting a pancreas cell, comprising, one or more the following steps, e.g. contacting a sample comprising cells with a binding partner (e.g. an antibody, an Fab fragment, a single-chain antibody, an aptamer) specific for a polypeptide coded for by a polypeptide of Table 20, or a mammalian homolog thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding. Protein binding assays can be accomplished routinely, e.g., using immunocytochemistry, ELISA format, Western blots, etc. Useful epitopes include those exposed to the surface.

As indicated above, binding partners can be used to deliver agents specifically to the pancreas, e.g., for diagnostic, therapeutic, and prognostic purposes. Methods of delivering an agent to a pancreas cell can comprise, e.g., contacting a pancreas cell with an agent coupled to a binding partner specific for a polypeptide coding for a gene of Table 20, whereby said agent is delivered to said cell. Any type of agent can be used, including, therapeutic and imaging agents. Contact with the pancreas can be achieved in any effective manner, including by administering effective amounts of the agent to a host orally, parentally, locally, systemically, intravenously, etc. The phrase "an agent coupled to binding partner" indicates that the agent is associated with the binding partner in such a manner that it can be carried specifically to the target site. Coupling includes, chemical bonding, covalent bonding, noncovalent bonding (where such bonding is sufficient to carry the agent to the target), present in a liposome or in a lipid membrane, associated with a carrier, such as a polymeric carrier, etc. The agent can be directly linked to the binding partner, or via chemical linkers or spacers. Any cell expressing a polypeptide coded for by a gene of Table 20 can be targeted, including, e.g., pancreatic progenitor, exocrine, endocrine, secretory, acinar, islet, alpha, beta, delta, F, D1, enterochromaffin, etc.

Imaging of specific organs can be facilitated using tissue selective antibodies and other binding partners that selectively target contrast agents to a specific site in the body. Various imaging techniques have been used in this context, including, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintographic. A reporter agent can be conjugated or associated routinely with a binding partner. Ultrasound contrast agents combined with binding partners, such as antibodies, are described in, e.g., U.S. Pat. Nos, 6,264,917,

6,254,852, 6,245,318, and 6,139,819. MRI contrast agents, such as metal chelators, radionucleotides, paramagnetic ions, etc., combined with selective targeting agents are also described in the literature, e.g., in U.S. Pat. Nos. 6,280,706 and 6,221,334. The methods described therein can be used generally to associate a partner with an agent for any desired purpose. See, Bruehlmeier et al., *Nucl. Med. Biol.*, 29:321-327, 2002, for imaging pancreas using labeled receptor ligands. Antibodies and other ligands to receptors of the present invention can be used analogously.

A pancreas cell (see above for examples of pancreas cell types) can also be modulated in accordance with the present invention, e.g., by methods of modulating a pancreas cell, comprising, e.g., contacting said cell with an agent effective to modulate a gene of Table 20, or the biological activity of a polypeptide encoded thereby (e.g., SEQ ID NO 215, 217, 219, 221, 223, 225, 227, 229, 231, 233, 235, 237, 239, 241, 243, 245, 247, 249, 251, 253, and 255), or a mammalian homolog thereof, whereby said pancreas cell is modulated. Modulation as used throughout includes, e.g., stimulating, increasing, agonizing, activating, amplifying, blocking, inhibiting, reducing, antagonizing, preventing, decreasing, diminishing, etc.

An activity or function of the pancreas cell can be modulated, including, e.g., regulation of blood sugar, modulation of all aspects of the various secreted polypeptides (hormones, enzymes, etc.) produced by the pancreas, ligand-binding, exocytosis, amylase (and any of the other 20 or so digestive enzymes produced by the pancreas) secretion, autocrine responses, apoptosis (e.g., in the survival of beta-islet cells), etc.

The present invention also relates to polypeptide detection methods for assessing pancreas function, e.g., methods of assessing pancreas function, comprising, detecting a polypeptide coded for by a gene of Table 20, fragments thereof, polymorphisms thereof, in a body fluid, whereby the level of said polypeptide in said fluid is a measure of pancreas function. Pancreas function tests are usually performed to determine whether the pancreas is functioning normally as a way of diagnosing pancreas disease. Various tests are commonly used, including, e.g., assays for the presence of pancreatic enzymes in body fluids (e.g., amylase, serum lipase, serum trypsin-like immuoreactivity), studies of pancreatic structure (e.g., using x-ray, sonography, CT-scan, angiography, endoscopic retrograde cholangiopancreatography), and tests for pancreatic function (e.g., secretin-pancreozymin

(CCK) tst, Lundh meal test, Bz-Ty-PABA test, chymotrypsin in feces, etc). Detection of a polypeptide coded for by a gene of Table 20 provides an additional assessment tool, especially in diseases such as pancreatitis and pancreatic cancer where pancreatic markers can appear in the blood, stool, urine, and other body fluids. As with the other tests, elevated levels of said polypeptide in blood, or other fluids, can indicate impaired pancreas function. Values can be determined routinely, as they are for other markers , such as those mentioned above. Detecting can be performed routinely (see below), e.g., using an antibody which is specific for said polypeptide, by RIA, ELISA, or Western blot, etc., in analogy to the tests for pancreatic enzymes in body fluids.

Promoter sequences obtained from genes of the present invention can be utilized to selectively express heterologous genes in pancreas cells. Methods of expressing a heterologous polynucleotide in pancreas cells can comprise, e.g., expressing a nucleic acid construct in pancreas cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected SEQ ID NO 258, 261, 262, 265-267, 270-272, 275, 278, 279, 282-284, 287, 290-293, 296, 297, 303, 306, 309-314, 317-320, 323-326, 329, 332-333, 336-338, 341, and 344 as shown in Table 23. In addition to the cell lines mentioned below, the construct can be expressed in primary cells or in established cell lines.

The genes and polypeptides of Table 20 can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions of the pancreas as mentioned above. The present invention relates to methods of identifying a pancreatic disease or pancreatic disease-susceptibility, comprising, e.g., determining the association of a pancreatic disease or pancreatic disease-susceptibility with a nucleotide sequence present within the pancreatic gene complex. An association between a pancreas disease or disease-susceptibility and nucleotide sequence includes, e.g., establishing (or finding) a correlation (or relationship) between a DNA marker (e.g., gene, VNTR, polymorphism, EST, etc.) and a particular disease state. Once a relationship is identified, the DNA marker can be utilized in diagnostic tests and as a drug target.

Human linkage maps can be constructed to establish a relationship between the cytogenetic locus as shown in Table 22 and a pancreatic disease or condition. Typically, polymorphic molecular markers (e.g., STRP's, SNP's, RFLP's, VNTR's) are identified

within the region, linkage and map distance between the markers is then established, and then linkage is established between phenotype and the various individual molecular markers. Maps can be produced individual family, selected populations, patient populations, etc. In general, these methods involve identifying a marker associated with the disease (e.g., identifying a polymorphism in a family which is linked to the disease) and then analyzing the surrounding DNA to identity the gene responsible for the phenotype.

Nucleic acids

A mammalian polynucleotide, or fragment thereof, of the present invention is a polynucleotide having a nucleotide sequence obtainable from a natural source. When the species name is used, e.g., a human, it indicates that the polynucleotide or polypeptide is obtainable from a natural source. It therefore includes naturally-occurring normal, naturally-occurring mutant, and naturally-occurring polymorphic alleles (e.g., SNPs), differentially-spliced transcripts, splice-variants, etc. By the term "naturally-occurring," it is meant that the polynucleotide is obtainable from a natural source, e.g., animal tissue and cells, body fluids, tissue culture cells, forensic samples. Natural sources include, e.g., living cells obtained from tissues and whole organisms, tumors, cultured cell lines, including primary and immortalized cell lines. Naturally-occurring mutations can include deletions (e.g., a truncated amino- or carboxy-terminus), substitutions, inversions, or additions of nucleotide sequence. These genes can be detected and isolated by polynucleotide hybridization according to methods which one skilled in the art would know, e.g., as discussed below.

A polynucleotide according to the present invention can be obtained from a variety of different sources. It can be obtained from DNA or RNA, such as polyadenylated mRNA or total RNA, e.g., isolated from tissues, cells, or whole organism. The polynucleotide can be obtained directly from DNA or RNA, from a cDNA library, from a genomic library, etc. The polynucleotide can be obtained from a cell or tissue (e.g., from an embryonic or adult tissues) at a particular stage of development, having a desired genotype, phenotype, disease status, etc.

The polynucleotides described herein can be partial sequences that correspond to full-length, naturally-occurring transcripts. The present invention includes, as well, full-length polynucleotides that comprise these partial sequences, e.g., genomic DNAs and polynucleotides comprising a start and stop codon, a start codon and a polyA tail, a

transcription start and a polyA tail, etc. These sequences can be obtained by any suitable method, e.g., using a partial sequence as a probe to select a full-length cDNA from a library containing full-length inserts. A polynucleotide which "codes without interruption" refers to a polynucleotide having a continuous open reading frame ("ORF") as compared to an ORF which is interrupted by introns or other noncoding sequences.

Polynucleotides and polypeptides can be excluded as compositions from the present invention if, e.g., listed in a publicly available databases on the day this application was filed and/or disclosed in a patent application having an earlier filing or priority date than this application and/or conceived and/or reduced to practice earlier than a polynucleotide in this application.

As described herein, the phrase "an isolated polynucleotide which is SEQ ID NO," or "an isolated polynucleotide which is selected from SEQ ID NO," refers to an isolated nucleic acid molecule from which the recited sequence was derived (e.g., a cDNA derived from mRNA; cDNA derived from genomic DNA). Because of sequencing errors, typographical errors, etc., the actual naturally-occurring sequence may differ from a SEQ ID listed herein. Thus, the phrase indicates the specific molecule from which the sequence was derived, rather than a molecule having that exact recited nucleotide sequence, analogously to how a culture depository number refers to a specific cloned fragment in a cryotube.

As explained in more detail below, a polynucleotide sequence of the invention can contain the complete sequence as shown herein, degenerate sequences thereof, anti-sense, muteins thereof, genes comprising said sequences, full-length cDNAs comprising said sequences, complete genomic sequences, fragments thereof, homologs, primers, nucleic acid molecules which hybridize thereto, derivatives thereof , etc.

Genomic

The present invention also relates genomic DNA from which the polynucleotides of the present invention can be derived. A genomic DNA coding for a human, mouse, or other mammalian polynucleotide, can be obtained routinely, for example, by screening a genomic library (e.g., a YAC library) with a polynucleotide of the present invention, or by searching nucleotide databases, such as GenBank and EMBL, for matches. Promoter and other regulatory regions (including both 5' and 3' regions, as well introns) can be identified

upstream or downstream of coding and expressed RNAs, and assayed routinely for activity, e.g., by joining to a reporter gene (e.g., CAT, GFP, alkaline phosphatase, luciferase, galatosidase). A promoter obtained from a tissue selective gene can be used, e.g., in gene therapy to obtain tissue-specific expression of a heterologous gene (e.g., coding for a therapeutic product or cytotoxin). 5' and 3' sequences (including, UTRs and introns) can be used to modulate or regulate stability, transcription, and translation of nucleic acids, including the sequence to which is attached in nature, as well as heterologous nucleic acids.

Constructs

A polynucleotide of the present invention can comprise additional polynucleotide sequences, e.g., sequences to enhance expression, detection, uptake, cataloging, tagging, etc. A polynucleotide can include only coding sequence; a coding sequence and additional non-naturally occurring or heterologous coding sequence (e.g., sequences coding for leader, signal, secretory, targeting, enzymatic, fluorescent, antibiotic resistance, and other functional or diagnostic peptides); coding sequences and non-coding sequences, e.g., untranslated sequences at either a 5' or 3' end, or dispersed in the coding sequence, e.g., introns.

A polynucleotide according to the present invention also can comprise an expression control sequence operably linked to a polynucleotide as described above. The phrase "expression control sequence" means a polynucleotide sequence that regulates expression of a polypeptide coded for by a polynucleotide to which it is functionally ("operably") linked. Expression can be regulated at the level of the mRNA or polypeptide. Thus, the expression control sequence includes mRNA-related elements and protein-related elements. Such elements include promoters, enhancers (viral or cellular), ribosome binding sequences, transcriptional terminators, etc. An expression control sequence is operably linked to a nucleotide coding sequence when the expression control sequence is positioned in such a manner to effect or achieve expression of the coding sequence. For example, when a promoter is operably linked 5' to a coding sequence, expression of the coding sequence is driven by the promoter. Expression control sequences can include an initiation codon and additional nucleotides to place a partial nucleotide sequence of the present invention in-frame in order to produce a polypeptide (e.g., pET vectors from Promega have been designed to permit a molecule to be inserted into all three reading frames to identify the one that results

in polypeptide expression). Expression control sequences can be heterologous or endogenous to the normal gene.

A polynucleotide of the present invention can also comprise nucleic acid vector sequences, e.g., for cloning, expression, amplification, selection, etc. Any effective vector can be used. A vector is, e.g., a polynucleotide molecule which can replicate autonomously in a host cell, e.g., containing an origin of replication. Vectors can be useful to perform manipulations, to propagate, and/or obtain large quantities of the recombinant molecule in a desired host. A skilled worker can select a vector depending on the purpose desired, e.g., to propagate the recombinant molecule in bacteria, yeast, insect, or mammalian cells. The following vectors are provided by way of example. Bacterial: pQE70, pQE60, pQE-9 (Qiagen), pBS, pD10, Phagescript, phiX174, pBK Phagemid, pNH8A, pNH16a, pNH18Z, pNH46A (Stratagene); Bluescript KS+II (Stratagene); ptrc99a, pKK223-3, pKK233-3, pDR54 0, pRIT5 (Pharmacia). Eukaryotic: PWLNEO, pSV2CAT, pOG44, pXT1, pSG (Stratagene), pSVK3, PBPV, PMSG, pSVL (Pharmacia), pCR2.1/TOPO, pCRII/TOPO, pCR4/TOPO, pTrcHisB, pCMV6-XL4, etc. However, any other vector, e.g., plasmids, viruses, or parts thereof, may be used as long as they are replicable and viable in the desired host. The vector can also comprise sequences which enable it to replicate in the host whose genome is to be modified.

Hybridization

Polynucleotide hybridization, as discussed in more detail below, is useful in a variety of applications, including, in gene detection methods, for identifying mutations, for making mutations, to identify homologs in the same and different species, to identify related members of the same gene family, in diagnostic and prognostic assays, in therapeutic applications (e.g., where an antisense polynucleotide is used to inhibit expression), etc.

The ability of two single-stranded polynucleotide preparations to hybridize together is a measure of their nucleotide sequence complementarity, e.g., base-pairing between nucleotides, such as A-T, G-C, etc. The invention thus also relates to polynucleotides, and their complements, which hybridize to a polynucleotide comprising a nucleotide sequence as set forth herein and genomic sequences thereof. A nucleotide sequence hybridizing to the latter sequence will have a complementary polynucleotide strand, or act as a template for one

in the presence of a polymerase (i.e., an appropriate polynucleotide synthesizing enzyme). The present invention includes both strands of polynucleotide, e.g., a sense strand and an anti-sense strand.

Hybridization conditions can be chosen to select polynucleotides which have a desired amount of nucleotide complementarity with the nucleotide sequences set forth in herein and genomic sequences thereof. A polynucleotide capable of hybridizing to such sequence, preferably, possesses, e.g., about 70%, 75%, 80%, 85%, 87%, 90%, 92%, 95%, 97%, 99%, or 100% complementarity, between the sequences. The present invention particularly relates to polynucleotide sequences which hybridize to the nucleotide sequences set forth in the attached sequence disclosure or genomic sequences thereof, under low or high stringency conditions. These conditions can be used, e.g., to select corresponding homologs in non-human species.

Polynucleotides which hybridize to polynucleotides of the present invention can be selected in various ways. Filter-type blots (i.e., matrices containing polynucleotide, such as nitrocellulose), glass chips, and other matrices and substrates comprising polynucleotides (short or long) of interest, can be incubated in a prehybridization solution (e.g., 6X SSC, 0.5% SDS, 100 µg/ml denatured salmon sperm DNA, 5X Denhardt's solution, and 50% formamide), at 22-68°C, overnight, and then hybridized with a detectable polynucleotide probe under conditions appropriate to achieve the desired stringency. In general, when high homology or sequence identity is desired, a high temperature can be used (e.g., 65 °C). As the homology drops, lower washing temperatures are used. For salt concentrations, the lower the salt concentration, the higher the stringency. The length of the probe is another consideration. Very short probes (e.g., less than 100 base pairs) are washed at lower temperatures, even if the homology is high. With short probes, formamide can be omitted. See, e.g., *Current Protocols in Molecular Biology*, Chapter 6, Screening of Recombinant Libraries; Sambrook et al., *Molecular Cloning*, 1989, Chapter 9.

For instance, high stringency conditions can be achieved by incubating the blot overnight (e.g., at least 12 hours) with a polynucleotide probe in a hybridization solution containing, e.g., about 5X SSC, 0.1-0.5% SDS, 100 µg/ml denatured salmon sperm DNA and 50% formamide, at 42°C, or hybridizing at 42°C in 5X SSPE, 0.1-0.5% SDS, and 50%

formamide, 100 µg/ml denatured salmon sperm DNA, and washing at 65°C in 0.1% SSC and 0.1% SDS.

Blots can be washed at high stringency conditions that allow, e.g., for less than 5% bp mismatch (e.g., wash twice in 0.1% SSC and 0.1% SDS for 30 min at 65°C), i.e., selecting sequences having 95% or greater sequence identity.

Other non-limiting examples of high stringency conditions includes a final wash at 65°C in aqueous buffer containing 30 mM NaCl and 0.5% SDS. Another example of high stringent conditions is hybridization in 7% SDS, 0.5 M $NaPO_4$, pH 7, 1 mM EDTA at 50°C, e.g., overnight, followed by one or more washes with a 1% SDS solution at 42°C. Whereas high stringency washes can allow for, e.g., less than 10%, less than 5% mismatch, etc., reduced or low stringency conditions can permit up to 20% nucleotide mismatch. Hybridization at low stringency can be accomplished as above, but using lower formamide conditions, lower temperatures and/or lower salt concentrations, as well as longer periods of incubation time.

Hybridization can also be based on a calculation of melting temperature (Tm) of the hybrid formed between the probe and its target, as described in Sambrook et al.. Generally, the temperature Tm at which a short oligonucleotide (containing 18 nucleotides or fewer) will melt from its target sequence is given by the following equation: Tm = (number of A's and T's) x 2°C + (number of C's and G's) x 4°C. For longer molecules, $Tm = 81.5 + 16.6 \log_{10}[Na^+] + 0.41(\%GC) - 600/N$ where $[Na^+]$ is the molar concentration of sodium ions, %GC is the percentage of GC base pairs in the probe, and N is the length. Hybridization can be carried out at several degrees below this temperature to ensure that the probe and target can hybridize. Mismatches can be allowed for by lowering the temperature even further.

Stringent conditions can be selected to isolate sequences, and their complements, which have, e.g., at least about 90%, 95%, or 97% nucleotide complementarity between the probe (e.g., a short polynucleotide of the sequences disclosed herein or genomic sequences thereof) and a target polynucleotide.

Other homologs of polynucleotides of the present invention can be obtained from mammalian and non-mammalian sources according to various methods. For example, hybridization with a polynucleotide can be employed to select homologs, e.g., as described in Sambrook et al., *Molecular Cloning*, Chapter 11, 1989. Such homologs can have varying

amounts of nucleotide and amino acid sequence identity and similarity to such polynucleotides of the present invention. Mammalian organisms include, e.g., mice, rats, monkeys, pigs, cows, etc. Non-mammalian organisms include, e.g., vertebrates, invertebrates, zebra fish, chicken, Drosophila, C. elegans, Xenopus, yeast such as S. pombe, S. cerevisiae, roundworms, prokaryotes, plants, Arabidopsis, artemia, viruses, etc. The degree of nucleotide sequence identity between human and mouse can be about, e.g. 70% or more, 85% or more for open reading frames, etc.

Alignment

Alignments can be accomplished by using any effective algorithm. For pairwise alignments of DNA sequences, the methods described by Wilbur-Lipman (e.g., Wilbur and Lipman, *Proc. Natl. Acad. Sci.*, 80:726-730, 1983) or Martinez/Needleman-Wunsch (e.g., Martinez, *Nucleic Acid Res.*, 11:4629-4634, 1983) can be used. For instance, if the Martinez/Needleman-Wunsch DNA alignment is applied, the minimum match can be set at 9, gap penalty at 1.10, and gap length penalty at 0.33. The results can be calculated as a similarity index, equal to the sum of the matching residues divided by the sum of all residues and gap characters, and then multiplied by 100 to express as a percent. Similarity index for related genes at the nucleotide level in accordance with the present invention can be greater than 70%, 80%, 85%, 90%, 95%, 99%, or more. Pairs of protein sequences can be aligned by the Lipman-Pearson method (e.g., Lipman and Pearson, *Science*, 227:1435-1441, 1985) with k-tuple set at 2, gap penalty set at 4, and gap length penalty set at 12. Results can be expressed as percent similarity index, where related genes at the amino acid level in accordance with the present invention can be greater than 65%, 70%, 75%, 80%, 85%, 90%, 95%, 99%, or more. Various commercial and free sources of alignment programs are available, e.g., MegAlign by DNA Star, BLAST (National Center for Biotechnology Information), BCM (Baylor College of Medicine) Launcher, etc. BLAST can be used to calculate amino acid sequence identity, amino acid sequence homology, and nucleotide sequence identity. These calculations can be made along the entire length of each of the target sequences which are to be compared.

After two sequences have been aligned, a "percent sequence identity" can be determined. For these purposes, it is convenient to refer to a Reference Sequence and a

Compared Sequence, where the Compared Sequence is *compared* to the Reference Sequence. Percent sequence identity can be determined according to the following formula: Percent Identity = 100 [1-(C/R)], wherein C is the number of differences between the Reference Sequence and the Compared Sequence over the length of alignment between the Reference Sequence and the Compared Sequence where (i) each base or amino acid in the Reference Sequence that does not have a corresponding aligned base or amino acid in the Compared Sequence, (ii) each gap in the Reference Sequence, (iii) each aligned base or amino acid in the Reference Sequence that is different from an aligned base or amino acid in the Compared Sequence, constitutes a difference; and R is the number of bases or amino acids in the Reference Sequence over the length of the alignment with the Compared Sequence with any gap created in the Reference Sequence also being counted as a base or amino acid.

Percent sequence identity can also be determined by other conventional methods, e.g., as described in Altschul et al., *Bull. Math. Bio.* 48: 603-616, 1986 and Henikoff and Henikoff, *Proc. Natl. Acad. Sci.* USA 89:10915-10919, 1992.

Specific polynucleotide probes

A polynucleotide of the present invention can comprise any continuous nucleotide sequence described herein, sequences which share sequence identity thereto, or complements thereof. The term "probe" refers to any substance that can be used to detect, identify, isolate, etc., another substance. A polynucleotide probe is comprised of nucleic acid can be used to detect, identify, etc., other nucleic acids, such as DNA and RNA.

These polynucleotides can be of any desired size that is effective to achieve the specificity desired. For example, a probe can be from about 7 or 8 nucleotides to several thousand nucleotides, depending upon its use and purpose. For instance, a probe used as a primer PCR can be shorter than a probe used in an ordered array of polynucleotide probes. Probe sizes vary, and the invention is not limited in any way by their size, e.g., probes can be from about 7-2000 nucleotides, 7-1000, 8-700, 8-600, 8-500, 8-400, 8-300, 8-150, 8-100, 8-75, 7-50, 10-25, 14-16, at least about 8, at least about 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, or more, etc. The polynucleotides can have non-naturally-occurring nucleotides, e.g., inosine, AZT, 3TC, etc. The polynucleotides can have 100% sequence identity or complementarity to a sequence disclosed herein, or it can have mismatches or

nucleotide substitutions, e.g., 1, 2, 3, 4, or 5 substitutions. The probes can be single-stranded or double-stranded.

In accordance with the present invention, a polynucleotide can be present in a kit, where the kit includes, e.g., one or more polynucleotides, a desired buffer (e.g., phosphate, tris, etc.), detection compositions, RNA or cDNA from different tissues to be used as controls, libraries, etc. The polynucleotide can be labeled or unlabeled, with radioactive or non-radioactive labels as known in the art. Kits can comprise one or more pairs of polynucleotides for amplifying nucleic acids specific for tissue selective genes, e.g., comprising a forward and reverse primer effective in PCR. These include both sense and anti-sense orientations. For instance, in PCR-based methods (such as RT-PCR), a pair of primers are typically used, one having a sense sequence and the other having an antisense sequence.

Another aspect of the present invention is a nucleotide sequence that is specific to, or for, a selective polynucleotide. The phrases "specific for" or "specific to" a polynucleotide have a functional meaning that the polynucleotide can be used to identify the presence of one or more target genes in a sample and distinguish them from non-target genes. It is specific in the sense that it can be used to detect polynucleotides above background noise ("non-specific binding"). A specific sequence is a defined order of nucleotides (or amino acid sequences, if it is a polypeptide sequence) which occurs in the polynucleotide, e.g., in the nucleotide sequences of the present invention, and which is characteristic of that target sequence, and substantially no non-target sequences. A probe or mixture of probes can comprise a sequence or sequences that are specific to a plurality of target sequences, e.g., where the sequence is a consensus sequence, a functional domain, etc., e.g., capable of recognizing a family of related genes. Such sequences can be used as probes in any of the methods described herein or incorporated by reference. Both sense and antisense nucleotide sequences are included. A specific polynucleotide according to the present invention can be determined routinely.

A polynucleotide comprising a specific sequence can be used as a hybridization probe to identify the presence of, e.g., human or mouse polynucleotide, in a sample comprising a mixture of polynucleotides, e.g., on a Northern blot. Hybridization can be performed under high stringent conditions (see, above) to select polynucleotides (and their complements which

can contain the coding sequence) having at least 90%, 95%, 99%, etc., identity (i.e., complementarity) to the probe, but less stringent conditions can also be used. A specific polynucleotide sequence can also be fused in-frame, at either its 5' or 3' end, to various nucleotide sequences as mentioned throughout the patent, including coding sequences for enzymes, detectable markers, GFP, etc, expression control sequences, etc.

A polynucleotide probe, especially one that is specific to a polynucleotide of the present invention, can be used in gene detection and hybridization methods as already described. In one embodiment, a specific polynucleotide probe can be used to detect whether a particular tissue or cell-type is present in a target sample. To carry out such a method, a selective polynucleotide can be chosen which is characteristic of the desired target tissue. Such polynucleotide is preferably chosen so that it is expressed or displayed in the target tissue, but not in other tissues which are present in the sample. For instance, if detection of pancreas, or kidney, it may not matter whether the selective polynucleotide is expressed in other tissues, as long as it is not expressed in cells normally present in blood, e.g., peripheral blood mononuclear cells. Starting from the selective polynucleotide, a specific polynucleotide probe can be designed which hybridizes (if hybridization is the basis of the assay) under the hybridization conditions to the selective polynucleotide, whereby the presence of the selective polynucleotide can be determined.

Probes which are specific for polynucleotides of the present invention can also be prepared using involve transcription-based systems, e.g., incorporating an RNA polymerase promoter into a selective polynucleotide of the present invention, and then transcribing anti-sense RNA using the polynucleotide as a template. See, e.g., U.S. Pat. No. 5,545,522.

Polynucleotide composition

A polynucleotide according to the present invention can comprise, e.g., DNA, RNA, synthetic polynucleotide, peptide polynucleotide, modified nucleotides, dsDNA, ssDNA, ssRNA, dsRNA, and mixtures thereof. A polynucleotide can be single- or double-stranded, triplex, DNA:RNA, duplexes, comprise hairpins, and other secondary structures, etc. Nucleotides comprising a polynucleotide can be joined via various known linkages, e.g., ester, sulfamate, sulfamide, phosphorothioate, phosphoramidate, methylphosphonate, carbamate, etc., depending on the desired purpose, e.g., resistance to nucleases, such as

RNAse H, improved in vivo stability, etc. See, e.g., U.S. Pat. No. 5,378,825. Any desired nucleotide or nucleotide analog can be incorporated, e.g., 6-mercaptoguanine, 8-oxo-guanine, etc.

Various modifications can be made to the polynucleotides, such as attaching detectable markers (avidin, biotin, radioactive elements, fluorescent tags and dyes, energy transfer labels, energy-emitting labels, binding partners, etc.) or moieties which improve hybridization, detection, and/or stability. The polynucleotides can also be attached to solid supports, e.g., nitrocellulose, magnetic or paramagnetic microspheres (e.g., as described in U.S. Pat. No. 5,411,863; U.S. Pat. No. 5,543,289; for instance, comprising ferromagnetic, supermagnetic, paramagnetic, superparamagnetic, iron oxide and polysaccharide), nylon, agarose, diazotized cellulose, latex solid microspheres, polyacrylamides, etc., according to a desired method. See, e.g., U.S. Pat. Nos. 5,470,967, 5,476,925, and 5,478,893.

Polynucleotide according to the present invention can be labeled according to any desired method. The polynucleotide can be labeled using radioactive tracers such as ^{32}P, ^{35}S, ^{3}H, or ^{14}C, to mention some commonly used tracers. The radioactive labeling can be carried out according to any method, such as, for example, terminal labeling at the 3' or 5' end using a radiolabeled nucleotide, polynucleotide kinase (with or without dephosphorylation with a phosphatase) or a ligase (depending on the end to be labeled). A non-radioactive labeling can also be used, combining a polynucleotide of the present invention with residues having immunological properties (antigens, haptens), a specific affinity for certain reagents (ligands), properties enabling detectable enzyme reactions to be completed (enzymes or coenzymes, enzyme substrates, or other substances involved in an enzymatic reaction), or characteristic physical properties, such as fluorescence or the emission or absorption of light at a desired wavelength, etc.

Nucleic acid detection methods

Another aspect of the present invention relates to methods and processes for detecting tissue selective genes. Detection methods have a variety of applications, including for diagnostic, prognostic, forensic, and research applications. To accomplish gene detection, a polynucleotide in accordance with the present invention can be used as a "probe." The term "probe" or "polynucleotide probe" has its customary meaning in the art, e.g., a polynucleotide

which is effective to identify (e.g., by hybridization), when used in an appropriate process, the presence of a target polynucleotide to which it is designed. Identification can involve simply determining presence or absence, or it can be quantitative, e.g., in assessing amounts of a gene or gene transcript present in a sample. Probes can be useful in a variety of ways, such as for diagnostic purposes, to identify homologs, and to detect, quantitate, or isolate a polynucleotide of the present invention in a test sample.

Assays can be utilized which permit quantification and/or presence/absence detection of a target nucleic acid in a sample. Assays can be performed at the single-cell level, or in a sample comprising many cells, where the assay is "averaging" expression over the entire collection of cells and tissue present in the sample. Any suitable assay format can be used, including, but not limited to, e.g., Southern blot analysis, Northern blot analysis, polymerase chain reaction ("PCR") (e.g., Saiki et al., *Science*, 241:53, 1988; U.S. Pat. Nos. 4,683,195, 4,683,202, and 6,040,166; *PCR Protocols: A Guide to Methods and Applications*, Innis et al., eds., Academic Press, New York, 1990), reverse transcriptase polymerase chain reaction ("RT-PCR"), anchored PCR, rapid amplification of cDNA ends ("RACE") (e.g., Schaefer in *Gene Cloning and Analysis: Current Innovations*, Pages 99-115, 1997), ligase chain reaction ("LCR") (EP 320 308), one-sided PCR (Ohara et al., *Proc. Natl. Acad. Sci.*, 86:5673-5677, 1989), indexing methods (e.g., U.S. Pat. No. 5,508,169), *in situ* hybridization, differential display (e.g., Liang et al., *Nucl. Acid. Res.*, 21:3269-3275, 1993; U.S. Pat. Nos. 5,262,311, 5,599,672 and 5,965,409; WO97/18454; Prashar and Weissman, *Proc. Natl. Acad. Sci.*, 93:659-663, and U.S. Pat. Nos. 6,010,850 and 5,712,126; Welsh et al., *Nucleic Acid Res.*, 20:4965-4970, 1992, and U.S. Pat. No. 5,487,985) and other RNA fingerprinting techniques, nucleic acid sequence based amplification ("NASBA") and other transcription based amplification systems (e.g., U.S. Pat. Nos. 5,409,818 and 5,554,527; WO 88/10315), polynucleotide arrays (e.g., U.S. Pat. Nos. 5,143,854, 5,424,186; 5,700,637, 5,874,219, and 6,054,270; PCT WO 92/10092; PCT WO 90/15070), Qbeta Replicase (PCT/US87/00880), Strand Displacement Amplification ("SDA"), Repair Chain Reaction ("RCR"), nuclease protection assays, subtraction-based methods, Rapid-Scan™, etc. Additional useful methods include, but are not limited to, e.g., template-based amplification methods, competitive PCR (e.g., U.S. Pat. No. 5,747,251), redox-based assays (e.g., U.S. Pat. No. 5,871,918), Taqman-based assays (e.g., Holland et al., *Proc. Natl. Acad, Sci.*, 88:7276-7280, 1991; U.S. Pat. Nos.

5,210,015 and 5,994,063), real-time fluorescence-based monitoring (e.g., U.S. Pat. 5,928,907), molecular energy transfer labels (e.g., U.S. Pat. Nos. 5,348,853, 5,532,129, 5,565,322, 6,030,787, and 6,117,635; Tyagi and Kramer, *Nature Biotech.*, 14:303-309, 1996). Any method suitable for single cell analysis of gene or protein expression can be used, including in situ hybridization, immunocytochemistry, MACS, FACS, flow cytometry, etc. For single cell assays, expression products can be measured using antibodies, PCR, or other types of nucleic acid amplification (e.g., Brady et al., *Methods Mol. & Cell. Biol.* 2, 17-25, 1990; Eberwine et al., 1992, *Proc. Natl. Acad. Sci.*, 89, 3010-3014, 1992; U.S. Pat. No. 5,723,290). These and other methods can be carried out conventionally, e.g., as described in the mentioned publications.

Many of such methods may require that the polynucleotide is labeled, or comprises a particular nucleotide type useful for detection. The present invention includes such modified polynucleotides that are necessary to carry out such methods. Thus, polynucleotides can be DNA, RNA, DNA:RNA hybrids, PNA, etc., and can comprise any modification or substituent which is effective to achieve detection.

Detection can be desirable for a variety of different purposes, including research, diagnostic, prognostic, and forensic. For diagnostic purposes, it may be desirable to identify the presence or quantity of a polynucleotide sequence in a sample, where the sample is obtained from tissue, cells, body fluids, etc. In a preferred method as described in more detail below, the present invention relates to a method of detecting a polynucleotide comprising, contacting a target polynucleotide in a test sample with a polynucleotide probe under conditions effective to achieve hybridization between the target and probe; and detecting hybridization.

Any test sample in which it is desired to identify a polynucleotide or polypeptide thereof can be used, including, e.g., blood, urine, saliva, stool (for extracting nucleic acid, see, e.g., U.S. Pat. No. 6,177,251), swabs comprising tissue, biopsied tissue, tissue sections, cultured cells, etc.

Detection can be accomplished in combination with polynucleotide probes for other genes, e.g., genes which are expressed in other disease states, tissues, cells, such as brain, heart, kidney, spleen, thymus, liver, stomach, small intestine, colon, muscle, lung, testis, placenta, pituitary, thyroid, skin, adrenal gland, pancreas, salivary gland, uterus, ovary,

prostate gland, peripheral blood cells (T-cells, lymphocytes, etc.), embryo, breast, fat, adult and embryonic stem cells, etc.

Polynucleotides can be used in wide range of methods and compositions, including for detecting, diagnosing, staging, grading, assessing, prognosticating, etc. diseases and disorders associated with tissue selective genes, for monitoring or assessing therapeutic and/or preventative measures, in ordered arrays, etc. Any method of detecting genes and polynucleotides can be used; certainly, the present invention is not to be limited how such methods are implemented.

Along these lines, the present invention relates to methods of detecting polynucleotides of the present invention in a sample comprising nucleic acid. Such methods can comprise one or more the following steps in any effective order, e.g., contacting said sample with a polynucleotide probe under conditions effective for said probe to hybridize specifically to nucleic acid in said sample, and detecting the presence or absence of probe hybridized to nucleic acid in said sample, wherein said probe is a polynucleotide which is described herein, a polynucleotide having, e.g., about 70%, 80%, 85%, 90%, 95%, 99%, or more sequence identity thereto, effective or specific fragments thereof, or complements thereto. The detection method can be applied to any sample, e.g., cultured primary, secondary, or established cell lines, tissue biopsy, blood, urine, stool, cerebral spinal fluid, and other bodily fluids, for any purpose.

Contacting the sample with probe can be carried out by any effective means in any effective environment. It can be accomplished in a solid, liquid, frozen, gaseous, amorphous, solidified, coagulated, colloid, etc., mixtures thereof, matrix. For instance, a probe in an aqueous medium can be contacted with a sample which is also in an aqueous medium, or which is affixed to a solid matrix, or vice-versa.

Generally, as used throughout the specification, the term "effective conditions" means, e.g., the particular milieu in which the desired effect is achieved. Such a milieu, includes, e.g., appropriate buffers, oxidizing agents, reducing agents, pH, co-factors, temperature, ion concentrations, suitable age and/or stage of cell (such as, in particular part of the cell cycle, or at a particular stage where particular genes are being expressed) where cells are being used, culture conditions (including substrate, oxygen, carbon dioxide, etc.). When hybridization is the chosen means of achieving detection, the probe and sample can be

combined such that the resulting conditions are functional for said probe to hybridize specifically to nucleic acid in said sample.

The phrase "hybridize specifically" indicates that the hybridization between single-stranded polynucleotides is based on nucleotide sequence complementarity. The effective conditions are selected such that the probe hybridizes to a preselected and/or definite target nucleic acid in the sample. For instance, if detection of a polynucleotide set forth herein is desired, a probe can be selected which can hybridize to such target gene under high stringent conditions, without significant hybridization to other genes in the sample. To detect homologs of a polynucleotide set forth in herein, the effective hybridization conditions can be less stringent, and/or the probe can comprise codon degeneracy, such that a homolog is detected in the sample.

As already mentioned, the methods can be carried out by any effective process, e.g., by Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, *in situ* hybridization, etc., as indicated above. When PCR based techniques are used, two or more probes are generally used. One probe can be specific for a defined sequence which is characteristic of a selective polynucleotide, but the other probe can be specific for the selective polynucleotide, or specific for a more general sequence, e.g., a sequence such as polyA which is characteristic of mRNA, a sequence which is specific for a promoter, ribosome binding site, or other transcriptional features, a consensus sequence (e.g., representing a functional domain). For the former aspects, 5' and 3' probes (e.g., polyA, Kozak, etc.) are preferred which are capable of specifically hybridizing to the ends of transcripts. When PCR is utilized, the probes can also be referred to as "primers" in that they can prime a DNA polymerase reaction.

In addition to testing for the presence or absence of polynucleotides, the present ~~invention also~~ relates to determining the amounts at which polynucleotides of the present invention are expressed in sample and determining the differential expression of such polynucleotides in samples.. Such methods can involve substantially the same steps as described above for presence/absence detection, e.g., contacting with probe, hybridizing, and detecting hybridized probe, but using more quantitative methods and/or comparisons to standards.

The amount of hybridization between the probe and target can be determined by any suitable methods, e.g., PCR, RT-PCR, RACE PCR, Northern blot, polynucleotide microarrays, Rapid-Scan, etc., and includes both quantitative and qualitative measurements. For further details, see the hybridization methods described above and below. Determining by such hybridization whether the target is differentially expressed (e.g., up-regulated or down-regulated) in the sample can also be accomplished by any effective means. For instance, the target's expression pattern in the sample can be compared to its pattern in a known standard, such as in a normal tissue, or it can be compared to another gene in the same sample. When a second sample is utilized for the comparison, it can be a sample of normal tissue that is known not to contain diseased cells. The comparison can be performed on samples which contain the same amount of RNA (such as polyadenylated RNA or total RNA), or, on RNA extracted from the same amounts of starting tissue. Such a second sample can also be referred to as a control or standard. Hybridization can also be compared to a second target in the same tissue sample. Experiments can be performed that determine a ratio between the target nucleic acid and a second nucleic acid (a standard or control) , e.g., in a normal tissue. When the ratio between the target and control are substantially the same in a normal and sample, the sample is determined or diagnosed not to contain cells. However, if the ratio is different between the normal and sample tissues, the sample is determined to contain, e.g., kidney, pancreas, or immune cells. The approaches can be combined, and one or more second samples, or second targets can be used. Any second target nucleic acid can be used as a comparison, including "housekeeping" genes, such as beta-actin, alcohol dehydrogenase, or any other gene whose expression does not vary depending upon the disease status of the cell.

Methods of identifying polymorphisms, mutations, etc.

Polynucleotides of the present invention can also be utilized to identify mutant alleles, SNPs, gene rearrangements and modifications, and other polymorphisms of the wild-type gene. Mutant alleles, polymorphisms, SNPs, etc., can be identified and isolated from subjects with diseases that are known, or suspected to have, a genetic component. Identification of such genes can be carried out routinely (see, above for more guidance), e.g., using PCR, hybridization techniques, direct sequencing, mismatch reactions (see, e.g.,

above), RFLP analysis, SSCP (e.g., Orita et al., *Proc. Natl. Acad. Sci.*, 86:2766, 1992), etc., where a polynucleotide having a sequence selected from the polynucleotides of the present invention is used as a probe. The selected mutant alleles, SNPs, polymorphisms, etc., can be used diagnostically to determine whether a subject has, or is susceptible to a disorder associated with tissue selective genes disclosed herein, as well as to design therapies and predict the outcome of the disorder. Methods involve, e.g., diagnosing a disorder or determining susceptibility to a disorder, comprising, detecting the presence of a mutation in a gene represented by a polynucleotide selected from the sequences disclosed herein. The detecting can be carried out by any effective method, e.g., obtaining cells from a subject, determining the gene sequence or structure of a target gene (using, e.g., mRNA, cDNA, genomic DNA, etc), comparing the sequence or structure of the target gene to the structure of the normal gene, whereby a difference in sequence or structure indicates a mutation in the gene in the subject. Polynucleotides can also be used to test for mutations, SNPs, polymorphisms, etc., e.g., using mismatch DNA repair technology as described in U.S. Pat. No. 5,683,877; U.S. Pat. No. 5,656,430; Wu et al., *Proc. Natl. Acad. Sci.*, 89:8779-8783, 1992.

The present invention also relates to methods of detecting polymorphisms in tissue selective genes, comprising, e.g., comparing the structure of: genomic DNA comprising all or part of a tissue selective gene, mRNA comprising all or part of a tissue selective gene, cDNA comprising all or part of a tissue selective gene, or a polypeptide comprising all or part of a tissue selective gene, with the structure the polynucleotides set forth herein. The methods can be carried out on a sample from any source, e.g., cells, tissues, body fluids, blood, urine, stool, hair, egg, sperm,cerebral spinal fluid, biopy samples, serum, etc.

These methods can be implemented in many different ways. For example, "comparing the structure" steps ~~include, but~~ are not ~~limited to,~~ comparing restriction maps, nucleotide sequences, amino acid sequences, RFLPs, Dnase sites, DNA methylation fingerprints (e.g., U.S. Pat. No. 6,214,556), protein cleavage sites, molecular weights, electrophoretic mobilities, charges, ion mobility, etc., between standard and a test genes. The term "structure" can refer to any physical characteristics or configurations which can be used to distinguish between nucleic acids and polypeptides. The methods and instruments used to accomplish the comparing step depends upon the physical characteristics which are to be

compared. Thus, various techniques are contemplated, including, e.g., sequencing machines (both amino acid and polynucleotide), electrophoresis, mass spectrometer (U.S. Pat. Nos. 6,093,541, 6,002,127), liquid chromatography, HPLC, etc.

To carry out such methods, "all or part" of the gene or polypeptide can be compared. For example, if nucleotide sequencing is utilized, the entire gene can be sequenced, including promoter, introns, and exons, or only parts of it can be sequenced and compared, e.g., exon 1, exon 2, etc.

Mutagenesis

Mutated polynucleotide sequences of the present invention are useful for various purposes, e.g., to create mutations of the polypeptides they encode, to identify functional regions of genomic DNA, to produce probes for screening libraries, etc. Mutagenesis can be carried out routinely according to any effective method, e.g., oligonucleotide-directed (Smith, M., *Ann. Rev. Genet.* 19:423-463, 1985), degenerate oligonucleotide-directed (Hill et al., *Method Enzymology*, 155:558-568, 1987), region-specific (Myers et al., *Science*, 229:242-246, 1985; Derbyshire et al., *Gene*, 46:145, 1986; Ner et al., *DNA*, 7:127, 1988), linker-scanning (McKnight and Kingsbury, *Science*, 217:316-324, 1982), directed using PCR, recursive ensemble mutagenesis (Arkin and Yourvan, *Proc. Natl. Acad. Sci.*, 89:7811-7815, 1992), random mutagenesis (e.g., U.S. Pat. Nos. 5,096,815; 5,198,346; and 5,223,409), site-directed mutagenesis (e.g., Walder et al., *Gene*, 42:133, 1986; Bauer et al., *Gene*, 37:73, 1985; Craik, *Bio Techniques*, January 1985, 12-19; Smith et al., *Genetic Engineering: Principles and Methods*, Plenum Press, 1981), phage display (e.g., Lowman et al., *Biochem.* 30:10832-10837, 1991; Ladner et al., U.S. Pat. No. 5,223,409; Huse, WIPO Publication WO 92/06204), etc. Desired sequences can also be produced by the assembly of target sequences using mutually priming oligonucleotides (Uhlmann, *Gene*, 71:29-40, 1988). For directed mutagenesis methods, analysis of the three-dimensional structure of the polypeptide can be used to guide and facilitate making mutants which effect polypeptide activity. Sites of substrate-enzyme interaction or other biological activities can also be determined by analysis of crystal structure as determined by such techniques as nuclear magnetic resonance, crystallography or photoaffinity labeling. See, for example, de Vos et al., Science 255:306-312, 1992; Smith et al., J. Mol. Biol. 224:899-904, 1992; Wlodaver et al., FEBS Lett.

309:59-64, 1992.

In addition, libraries of genes and fragments thereof can be used for screening and selection of genes variants. For instance, a library of coding sequences can be generated by treating a double-stranded DNA with a nuclease under conditions where the nicking occurs, e.g., only once per molecule, denaturing the double-stranded DNA, renaturing it to for double-stranded DNA that can include sense/antisense pairs from different nicked products, removing single-stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting DNAs into an expression vector. By this method, expression libraries can be made comprising "mutagenized" tissue selective genes. The entire coding sequence or parts thereof can be used.

Polynucleotide expression, polypeptides produced thereby, and specific-binding partners thereto.

A polynucleotide according to the present invention can be expressed in a variety of different systems, in vitro and in vivo, according to the desired purpose. For example, a polynucleotide can be inserted into an expression vector, introduced into a desired host, and cultured under conditions effective to achieve expression of a polypeptide coded for by the polynucleotide, to search for specific binding partners. Effective conditions include any culture conditions which are suitable for achieving production of the polypeptide by the host cell, including effective temperatures, pH, medium, additives to the media in which the host cell is cultured (e.g., additives which amplify or induce expression such as butyrate, or methotrexate if the coding polynucleotide is adjacent to a dhfr gene), cycloheximide, cell densities, culture dishes, etc. A polynucleotide can be introduced into the cell by any effective method including, e.g., naked DNA, calcium phosphate precipitation, electroporation, injection, DEAE-Dextran mediated transfection, fusion with liposomes, association with agents which enhance its uptake into cells, viral transfection. A cell into which a polynucleotide of the present invention has been introduced is a transformed host cell. The polynucleotide can be extrachromosomal or integrated into a chromosome(s) of the host cell. It can be stable or transient. An expression vector is selected for its compatibility with the host cell. Host cells include, mammalian cells, e.g., COS, CV1, BHK, CHO, HeLa, LTK, NIH 3T3, insect cells, such as Sf9 (S. frugipeda) and Drosophila, bacteria, such as E.

coli, Streptococcus, bacillus, yeast, such as Sacharomyces, S. cerevisiae, fungal cells, plant cells, embryonic or adult stem cells (e.g., mammalian, such as mouse or human),

immune system cell lines, HH (ATCC CRL 2105), MOLT-4 (ATCC CRL 1582), MJ (ATCC CRL-8294), SK7 (ATCC HB-8584), SK8 (ATCC HB-8585), HM1 (HB-8586), H9 (ATCC HTB-176), HuT 78 (ATCC TIB-161), HuT 102 (ATCC TIB-162), Jurkat,

B-cell lines, B-cell precursor lines, NALM-36, B-cell and other lymphocyte lines immortalized with Epstein-Barr virus (transformed B lymphoblastoid), stromal cell lines, myelomas, HBM-Noda, WEHI231,

reticuloendothelial cells, endothelial cells, white blood cells, macrophages, antigen-resenting cells, lymphocytes, GDM-1 (ATCC CRL-2627), THP-1 (ATCC TIB-202), HL-60 (ATCC CCL-240), and derivatives thereof, including primary and established cell lines thereof,

kidney cell lines, 293, G-402 (ATCC CRL-1440), ACHN (ATCC CRL-1611), Vero (ATCC CCL-81), 786-O (ATCC CRL-1932), 769-P (ATCC CRL-1933), CCD 1103 KIDTr (ATCC CRL-2304), CCD 1105 KIDTr (ATCC CRL-2305), Hs 835.T (ATCC CRL-7569), Hs 926.T (ATCC CRL-7678), Caki-1 (ATCC HTB-46), Caki-2 (ATCC HTB-47), SW 839 (ATCC HTB-49), LLC-MK2 (ATCC CCL-7), BHK-21 (ATCC CCL-10), MDCK, CV-1, (ATCC CRL-1573), KNRK (ATCC CRL-1569), NRK-49F (ATCC CRL-1570), A-704 (ATCC HTB-45), etc., established and primary kidney cells,

pancreas cell lines, , insulinoma cell lines, INS-H1, MIN6N8, RIN 1046-38, RIN-5AH, RIN-A12, RINm5F, capan-1, capan-2, MIA PaCa-2 (ATCC CRL-1420), PANC-1 (ATCC CRL-1469), AsPC-1 (ATCC CRL-1682), SU-86.86 (ATCC CRL-1837), CFPAC-1 (ATCC CRL-1918), HPAF-II (ATCC CRL-1937), TGP61 (ATCC CRL-2135) and other TGP lines, SW 1990 (ATCC CRL-2172), Mpanc-96 (ATCC CRL-2380), MS1 VEGF (ATCC CRL-2460), Beta-TC-6 (ATCC CRL-11506), LTPA (ATCC CRL-2389), 266-6 (ATCC CRL-2151), MS1 (ATCC CRL-2779), SVR (ATCC CRL-2280), NIT-2 (ATCC CRL-2364), alphaTC1 Clone 9 (ATCC CRL-2350), ATCC CRL-1492, BxPC-3 (ATCC CRL-1687), HPAC (ATCC CRL-2119), U.S. Pat. Nos. 6,110743, 5,928,942, 5,888,816, 5,888,705, and 5,723,333, etc., established and primary pancreas cells (e.g., according to Hellerstrom et al., *Diabetes*, 28:769-76, 1979),

retinal cell lines, RF/6A (CRL 1780), ARPE-19 (CRL-2302), ARPE-19/HPV-16 (CRL-2502), Y79 (HTB-18), WERI-Rb-1 (HTB-169), RPE-J (CRL-2240), SO-Rb50 (retinoblastoma cell line), RBL, HER-Xho1-CC2, WERI-Rb24 (Sery et al., *J. Pediatr. Ophthalmol. Strabismus*, 4:212-217, 1990), WERI-Rb27 (Sery et al., *J. Pediatr. Ophthalmol. Strabismus*, 4:212-217, 1990), HXO-Rb44, fetal retina cells, retinoblastoma cells, choroidal endothelial cells (e.g., Chor 55), etc., established and primary retinal cells (For other cell lines and methods thereof, see, also, Griege et al, *Differentiation*, 45:250-7, 1990; Bernstein et al., *Invest. Ophthalmol. Vis. Sci.*, 35:3931-3937, 1994; Howes et al., *Invest. Ophthalmol. Vis. Sci.*, 35:342-351, 1994).

Expression control sequences are similarly selected for host compatibility and a desired purpose, e.g., high copy number, high amounts, induction, amplification, controlled expression. Other sequences which can be employed include enhancers such as from SV40, CMV, RSV, inducible promoters, cell-type specific elements, or sequences which allow selective or specific cell expression. Promoters that can be used to drive its expression, include, e.g., the endogenous promoter, MMTV, SV40, trp, lac, tac, or T7 promoters for bacterial hosts; or alpha factor, alcohol oxidase, or PGH promoters for yeast. RNA promoters can be used to produced RNA transcripts, such as T7 or SP6. See, e.g., Melton et al., *Polynucleotide Res.*, 12(18):7035-7056, 1984; Dunn and Studier. *J. Mol. Bio.*, 166:477-435, 1984; U.S. Pat. No. 5,891,636; Studier et al., *Gene Expression Technology, Methods in Enzymology*, 85:60-89, 1987. In addition, as discussed above, translational signals (including in-frame insertions) can be included.

When a polynucleotide is expressed as a heterologous gene in a transfected cell line, the gene is introduced into a cell as described above, under effective conditions in which the gene is expressed. The term "heterologous" means that the gene has been introduced into the cell line by the "hand-of-man." Introduction of a gene into a cell line is discussed above. The transfected (or transformed) cell expressing the gene can be lysed or the cell line can be used intact.

For expression and other purposes, a polynucleotide can contain codons found in a naturally-occurring gene, transcript, or cDNA, for example, e.g., as set forth in herein or it can contain degenerate codons coding for the same amino acid sequences. For instance,

it may be desirable to change the codons in the sequence to optimize the sequence for expression in a desired host. See, e.g., U.S. Pat. Nos. 5,567,600 and 5,567,862.

A polypeptide according to the present invention can be recovered from natural sources, transformed host cells (culture medium or cells) according to the usual methods, including, detergent extraction (e.g., non-ionic detergent, Triton X-100, CHAPS, octylglucoside, Igepal CA-630), ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, hydroxyapatite chromatography, lectin chromatography, gel electrophoresis. Protein refolding steps can be used, as necessary, in completing the configuration of the mature protein. Finally, high performance liquid chromatography (HPLC) can be employed for purification steps. Another approach is express the polypeptide recombinantly with an affinity tag (Flag epitope, HA epitope, myc epitope, 6xHis, maltose binding protein, chitinase, etc) and then purify by anti-tag antibody-conjugated affinity chromatography.

The present invention also relates to specific-binding partners. These include antibodies which are specific for polypeptides encoded by polynucleotides of the present invention, as well as other binding-partners which interact with polynucleotides and polypeptides of the present invention. Protein-protein interactions between polypeptides and binding partners can be identified using any suitable methods, e.g., protein binding assays (e.g., filtration assays, chromatography, etc.) , yeast two-hybrid system (Fields and Song, *Nature*, 340: 245-247, 1989), protein arrays, gel-shift assays, FRET (fluorescence resonance energy transfer) assays, etc. Nucleic acid interactions (e.g., protein-DNA or protein-RNA) can be assessed using gel-shift assays, e.g., as carried out in U.S. Pat. No. 6,333,407 and 5,789,538.

Antibodies, e.g., polyclonal, monoclonal, recombinant, chimeric, humanized, single-chain, Fab, and fragments thereof, can be prepared according to any desired method. Antibodies, and immune responses, can also be generated by administering naked DNA See, e.g., U.S. Pat. Nos. 5,703,055; 5,589,466; 5,580,859. Antibodies can be used from any source, including, goat, rabbit, mouse, chicken (e.g., IgY; see, Duan, W0/029444 for methods of making antibodies in avian hosts, and harvesting the antibodies from the eggs). An antibody specific for a polypeptide means that the antibody recognizes a defined sequence of

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amino acids within or including the polypeptide. Other specific binding partners include, e.g., aptamers and PNA. Antibodies can be prepared against specific epitopes or domains.

Antibodies can also be humanized, e.g., where they are to be used therapeutically. Methods for obtaining human antibodies, e.g., from transgenic mice are described, e.g., in Green et al., Nature Genet. 7:13 (1994); Lonberg et al., Nature 368:856 (1994); and Taylor et al., Int. Immunol. 6:579 (1994). Antibody fragments of the present invention can be prepared by any suitable method, Fab and Fc fragments. sinbgle-chain antibodies can also be used. Another form of an antibody fragment is a peptide coding for a single complementarity-determining region (CDR). CDR peptides ("minimal recognition units") can be obtained by constructing genes encoding the CDR of an antibody of interest.

The term "antibody" as used herein includes intact molecules as well as fragments thereof, such as Fab, F(ab')2, and Fv which are capable of binding to an epitopic determinant present in Bin1 polypeptide. Such antibody fragments retain some ability to selectively bind with its antigen or receptor. The term "epitope" refers to an antigenic determinant on an antigen to which the paratope of an antibody binds. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. Antibodies can be prepared against specific epitopes or polypeptide domains.

Antibodies which bind to polypeptides of the present invention can be prepared using an intact polypeptide or fragments containing small peptides of interest as the immunizing antigen. For example, it may be desirable to produce antibodies that specifically bind to the N- or C-terminal domains of the tissue selective polypeptides of the present invention. The polypeptide or peptide used to immunize an animal which is derived from translated cDNA or chemically synthesized which can be conjugated to a carrier protein, if desired. Such commonly used carriers which are chemically coupled to the immunizing peptide include keyhole limpet hemocyanin (KLH), thyroglobulin, bovine serum albumin (BSA), and tetanus toxoid.

Methods of detecting polypeptides

Polypeptides coded for by genes of the present invention can be detected, visualized, determined, quantitated, etc. according to any effective method. useful methods include, e.g., but are not limited to, immunoassays, RIA (radioimmunassay), ELISA, (enzyme-linked-immunosorbent assay), immunoflourescence, flow cytometry, histology, electron microscopy, light microscopy, in situ assays, immunoprecipitation, Western blot, etc.

Immunoassays may be carried in liquid or on biological support. For instance, a sample (e.g., blood, serum, stool, urine, cells, tissue,cerebral spinal fluid, body fluids, etc.) can be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose, or other solid support that is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled specific antibody. The solid phase support can then be washed with a buffer a second time to remove unbound antibody. The amount of bound label on solid support may then be detected by conventional means.

A "solid phase support or carrier" includes any support capable of binding an antigen, antibody, or other specific binding partner. Supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, and magnetite. A support material can have any structural or physical configuration. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads

One of the many ways in which gene peptide-specific antibody can be detectably labeled is by linking it to an enzyme and using it in an enzyme immunoassay (EIA). See, e.g., Voller, A., "The Enzyme Linked Immunosorbent Assay (ELISA)," 1978, Diagnostic Horizons 2, 1-7, Microbiological Associates Quarterly Publication, Walkersville, Md.); Voller, A. et al., 1978, J. Clin. Pathol. 31, 507-520; Butler, J. E., 1981, Meth. Enzymol. 73, 482-523; Maggio, E. (ed.), 1980, Enzyme Immunoassay, CRC Press, Boca Raton, Fla.. The enzyme which is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety that can be detected, for example, by spectrophotometric, fluorimetric or by visual means. Enzymes that can be used to detectably label the antibody include, but are not limited to, malate

dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, .alpha.-glycerophosphate, dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, .beta.-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. The detection can be accomplished by colorimetric methods that employ a chromogenic substrate for the enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

Detection may also be accomplished using any of a variety of other immunoassays. For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect peptides through the use of a radioimmunoassay (RIA). See, e.g., Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986. The radioactive isotope can be detected by such means as the use of a gamma counter or a scintillation counter or by autoradiography.

It is also possible to label the antibody with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, o-phthaldehyde and fluorescamine. The antibody can also be detectably labeled using fluorescence emitting metals such as those in the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antibody is then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of

luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

Diagnostic

The present invention also relates to methods and compositions for diagnosing a disorder, or determining susceptibility to a disorder, using polynucleotides, polypeptides, and specific-binding partners of the present invention to detect, assess, determine, etc., a tissue selective gene. In such methods, the gene can serve as a marker for the disorder, e.g., where the gene, when mutant, is a direct cause of the disorder; where the gene is affected by another gene(s) which is directly responsible for the disorder, e.g., when the gene is part of the same signaling pathway as the directly responsible gene; and, where the gene is chromosomally linked to the gene(s) directly responsible for the disorder, and segregates with it. Many other situations are possible. To detect, assess, determine, etc., a probe specific for the gene can be employed as described above and below. Any method of detecting and/or assessing the gene can be used, including detecting expression of the gene using polynucleotides, antibodies, or other specific-binding partners.

The phrase "diagnosing" indicates that it is determined whether the sample has the disorder. A "disorder" means, e.g., any abnormal condition as in a disease or malady. "Determining a subject's susceptibility to a disease or disorder" indicates that the subject is assessed for whether s/he is predisposed to get such a disease or disorder, where the predisposition is indicated by abnormal expression of the gene (e.g., gene mutation, gene expression pattern is not normal, etc.). Predisposition or susceptibility to a disease may result when a such disease is influenced by epigenetic, environmental, etc., factors. Diagnosing includes prenatal screening where samples from the fetus or embryo (e.g., via amniocentesis or CV sampling) are analyzed for the expression of the gene.

By the phrase "assessing expression of a gene or polynucleotide," it is meant that the functional status of the gene is evaluated. This includes, but is not limited to, measuring expression levels of said gene, determining the genomic structure of said gene, determining the mRNA structure of transcripts from said gene, or measuring the expression levels of polypeptide coded for by said gene. Thus, the term "assessing expression" includes evaluating the all aspects of the transcriptional and translational machinery of the gene. For

instance, if a promoter defect causes, or is suspected of causing, the disorder, then a sample can be evaluated (i.e., "assessed") by looking (e.g., sequencing or restriction mapping) at the promoter sequence in the gene, by detecting transcription products (e.g., RNA), by detecting translation product (e.g., polypeptide). Any measure of whether the gene is functional can be used, including, polypeptide, polynucleotide, and functional assays for the gene's biological activity.

In making the assessment, it can be useful to compare the results to a normal gene, e.g., a gene which is not associated with the disorder. The nature of the comparison can be determined routinely, depending upon how the assessing is accomplished. If, for example, the mRNA levels of a sample is detected, then the mRNA levels of a normal can serve as a comparison, or a gene which is known not to be affected by the disorder. Methods of detecting mRNA are well known, and discussed above, e.g., but not limited to, Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, etc. Similarly, if polypeptide production is used to evaluate the gene, then the polypeptide in a normal tissue sample can be used as a comparison, or, polypeptide from a different gene whose expression is known not to be affected by the disorder. These are only examples of how such a method could be carried out.

The genes and polypeptides of the present invention can be used to identify, detect, stage, determine the presence of, prognosticate, treat, study, etc., diseases and conditions as mentioned above. The present invention relates to methods of identifying a genetic basis for a disease or disease-susceptibility, comprising, e.g., determining the association of a disease or disease-susceptibility with a gene of the present invention. An association between a disease or disease-susceptibility and nucleotide sequence includes, e.g., establishing (or finding) a correlation (or relationship) between a DNA marker (e.g., gene, VNTR, ~~polymorphism~~, EST, etc.) and a particular disease state. Once a relationship is identified, the DNA marker can be utilized in diagnostic tests and as a drug target. Any region of the gene can be used as a source of the DNA marker, exons, introns, intergenic regions, etc.

Human linkage maps can be constructed to establish a relationship between a gene and a disease or condition. Typically, polymorphic molecular markers (e.g., STRP's, SNP's, RFLP's, VNTR's) are identified within the region, linkage and map distance between the markers is then established, and then linkage is established between phenotype and the

various individual molecular markers. Maps can be produced for an individual family, selected populations, patient populations, etc. In general, these methods involve identifying a marker associated with the disease (e.g., identifying a polymorphism in a family which is linked to the disease) and then analyzing the surrounding DNA to identity the gene responsible for the phenotype. See, e.g., Kruglyak et al., *Am. J. Hum. Genet.*, 58, 1347-1363, 1996; Matise et al., *Nat. Genet.*, 6(4):384-90, 1994.

Assessing the effects of therapeutic and preventative interventions (e.g., administration of a drug, chemotherapy, radiation, etc.) on disorders is a major effort in drug discovery, clinical medicine, and pharmacogenomics. The evaluation of therapeutic and preventative measures, whether experimental or already in clinical use, has broad applicability, e.g., in clinical trials, for monitoring the status of a patient, for analyzing and assessing animal models, and in any scenario involving disease treatment and prevention. Analyzing the expression profiles of polynucleotides of the present invention can be utilized as a parameter by which interventions are judged and measured. Treatment of a disorder can change the expression profile in some manner which is prognostic or indicative of the drug's effect on it. Changes in the profile can indicate, e.g., drug toxicity, return to a normal level, etc. Accordingly, the present invention also relates to methods of monitoring or assessing a therapeutic or preventative measure (e.g., chemotherapy, radiation, anti-neoplastic drugs, antibodies, etc.) in a subject having a disorder, or, susceptible to such a disorder, comprising, e.g., detecting the expression levels of one or more tissue selective genes. A subject can be a cell-based assay system, non-human animal model, human patient, etc. Detecting can be accomplished as described for the methods above and below. By "therapeutic or preventative intervention," it is meant, e.g., a drug administered to a patient, surgery, radiation, chemotherapy, and other measures taken to prevent, treat, or diagnose a disorder.

The present invention also relates to methods of using binding partners, such as antibodies, to deliver active agents to the tissue (e.g., kidney or pancreas or an immune cells) for a variety of different purposes, including, e.g., for diagnostic, therapeutic, and research purposes. Methods can involve delivering or administering an active agent to the tissue, comprising, e.g., administering to a subject in need thereof, an effective amount of an active agent coupled to a binding partner specific for a tissue selective polypeptide, wherein said binding partner is effective to deliver said active agent specifically to the target tissue.

Any type of active agent can be used in combination with it, including, therapeutic, cytotoxic, cytostatic, chemotherapeutic, anti-neoplastic, anti-proliferative, anti-biotic, etc., agents. A chemotherapeutic agent can be, e.g., DNA-interactive agent, alkylating agent, antimetabolite, tubulin-interactive agent, hormonal agent, hydroxyurea, Cisplatin, Cyclophosphamide, Altretamine, Bleomycin, Dactinomycin, Doxorubicin, Etoposide, Teniposide, paclitaxel, cytoxan, 2-methoxy-carbonyl-amino-benzimidazole, Plicamycin, Methotrexate, Fluorouracil, Fluorodeoxyuridin, CB3717, Azacitidine, Floxuridine, Mercapyopurine, 6-Thioguanine, Pentostatin, Cytarabine, Fludarabine, etc. Agents can also be contrast agents useful in imaging technology, e.g., X-ray, CT, CAT, MRI, ultrasound, PET, SPECT, and scintographic.

An active agent can be associated in any manner with a binding partner which is effective to achieve its delivery specifically to the target. Specific delivery or targeting indicates that the agent is provided to the tissue, without being substantially provided to other tissues. This is useful especially where an agent is toxic, and specific targeting to the tissue enables the majority of the toxicity to be aimed at the tissue, with as small as possible effect on other tissues in the body. The association of the active agent and the binding partner ("coupling") can be direct, e.g., through chemical bonds between the binding partner and the agent, or, via a linking agent, or the association can be less direct, e.g., where the active agent is in a liposome, or other carrier, and the binding partner is associated with the liposome surface. In such case, the binding partner can be oriented in such a way that it is able to bind to tissue selective polypeptide, e.g., exposed on the cell surface. Methods for delivery of DNA via a cell-surface receptor is described, e.g., in U.S. Pat. No. 6,339,139.

Identifying agent methods

The present invention also relates to methods of identifying agents, and the agents themselves, which modulate tissue selective genes. These agents can be used to modulate the biological activity of the polypeptide encoded for the gene, or the gene, itself. Agents which regulate the gene or its product are useful in variety of different environments, including as medicinal agents to treat or prevent disorders associated with genes and as research reagents to modify the function of tissues and cell.

Methods of identifying agents generally comprise steps in which an agent is placed in contact with the gene, its transcription product, its translation product, or other target, and then a determination is performed to assess whether the agent "modulates" the target. The specific method utilized will depend upon a number of factors, including, e.g., the target (i.e., is it the gene or polypeptide encoded by it), the environment (e.g., in vitro or in vivo), the composition of the agent, etc.

For modulating the expression of tissue selective genes, a method can comprise, in any effective order, one or more of the following steps, e.g., contacting a gene (e.g., in a cell population) with a test agent under conditions effective for said test agent to modulate the expression of tissue selective genes, and determining whether said test agent modulates said genes. An agent can modulate expression of a tissue selective gene at any level, including transcription (e.g., by modulating the promoter), translation, and/or perdurance of the nucleic acid (e.g., degradation, stability, etc.) in the cell.

For modulating the biological activity of polypeptides, a method can comprise, in any effective order, one or more of the following steps, e.g., contacting a polypeptide (e.g., in a cell, lysate, or isolated) with a test agent under conditions effective for said test agent to modulate the biological activity of said polypeptide, and determining whether said test agent modulates said biological activity.

Contacting a gene or polypeptide with the test agent can be accomplished by any suitable method and/or means that places the agent in a position to functionally control expression or biological activity. Functional control indicates that the agent can exert its physiological effect through whatever mechanism it works. The choice of the method and/or means can depend upon the nature of the agent and the condition and type of environment in which the gene or polypeptide is presented, e.g., lysate, isolated, or in a cell population (such as, *in vivo*, *in vitro*, organ explants, etc.). For instance, if the cell population is an *in vitro* cell culture, the agent can be contacted with the cells by adding it directly into the culture medium. If the agent cannot dissolve readily in an aqueous medium, it can be incorporated into liposomes, or another lipophilic carrier, and then administered to the cell culture. Contact can also be facilitated by incorporation of agent with carriers and delivery molecules and complexes, by injection, by infusion, etc.

Agents can be directed to, or targeted to, any part of the polypeptide which is

effective for modulating it. For example, agents, such as antibodies and small molecules, can be targeted to cell-surface, exposed, extracellular, ligand binding, functional, etc., domains of the polypeptide. Agents can also be directed to intracellular regions and domains, e.g., regions where the polypeptide couples or interacts with intracellular or intramembrane binding partners.

After the agent has been administered in such a way that it can gain access, it can be determined whether the test agent modulates expression or biological activity. Modulation can be of any type, quality, or quantity, e.g., increase, facilitate, enhance, up-regulate, stimulate, activate, amplify, augment, induce, decrease, down-regulate, diminish, lessen, reduce, etc. The modulatory quantity can also encompass any value, e.g., 1%, 5%, 10%, 50%, 75%, 1-fold, 2-fold, 5-fold, 10-fold, 100-fold, etc. To modulate expression means, e.g., that the test agent has an effect on its expression, e.g., to effect the amount of transcription, to effect RNA splicing, to effect translation of the RNA into polypeptide, to effect RNA or polypeptide stability, to effect polyadenylation or other processing of the RNA, to effect post-transcriptional or post-translational processing, etc. To modulate biological activity means, e.g., that a functional activity of the polypeptide is changed in comparison to its normal activity in the absence of the agent. This effect includes, increase, decrease, block, inhibit, enhance, etc.

A test agent can be of any molecular composition, e.g., chemical compounds, biomolecules, such as polypeptides, lipids, nucleic acids (e.g., antisense), carbohydrates, antibodies, ribozymes, double-stranded RNA, aptamers, etc. For example, if a polypeptide to be modulated is a cell-surface molecule, a test agent can be an antibody that specifically recognizes it and, e.g., causes the polypeptide to be internalized, leading to its down regulation on the surface of the cell. Such an effect does not have to be permanent, but can require the presence of the antibody to continue the down-regulatory effect. Antibodies can also be used to modulate the biological activity of a polypeptide in a lysate or other cell-free form.

Additional cell-based test systems suitable for the analysis of GPCR polypeptides are summarized in Marchese et al. (1999, Trends in Pharmacol. Sci. 20: 370-375) and comprise so-called "ligand screening assays." For example in yeast cells the pheromon receptor can be replaced by a GPCR according to the invention. The effect of test substances on the receptor

can be determined upon modulation of histidine synthesis, i.e. by growing in histidine-free medium. In addition using cells transfected with nucleic acids according to the invention it can be analyzed whether test substances mediate translocation of a detectable arrestins, for example of a arrestin-GFP-fusion protein. Moreover, it can be analyzed whether test substances mediate GPCR-mediated dispersion or aggregation of Xenopus laevis melanophores. Another test system utilizes the universal adapter G-protein G alphal6, which mobilizes Ca.sup.2+. Other screening test systems are described in Lemer et al., supra; WO96/41169; U.S. Pat. No. 5,482,835; WO99/06535; EP 0 939 902; WO99/66326; WO98/34948; EP 0 863 214; U.S. Pat. No. 5,882,944 and U.S. Pat. No. 5,891,641.

Therapeutics

Selective polynucleotides, polypeptides, and specific-binding partners thereto, can be utilized in therapeutic applications, especially to treat diseases and conditions described herein. Useful methods include, but are not limited to, immunotherapy (e.g., using specific-binding partners to polypeptides), vaccination (e.g., using a selective polypeptide or a naked DNA encoding such polypeptide), protein or polypeptide replacement therapy, gene therapy (e.g., germ-line correction, antisense), etc.

Various immunotherapeutic approaches can be used. For instance, unlabeled antibody that specifically recognizes a tissue-specific antigen can be used to stimulate the body to destroy or attack a cancer or other diseased tissue, to cause down-regulation, to produce complement-mediated lysis, to inhibit cell growth, etc., of target cells which display the antigen, e.g., analogously to how c-erbB-2 antibodies are used to treat breast cancer. In addition, antibody can be labeled or conjugated to enhance its deleterious effect, e.g., with radionuclides and other energy emitting entitities, toxins, such as ricin, exotoxin A (ETA), and diphtheria, cytotoxic or cytostatic agents, immunomodulators, chemotherapeutic agents, etc. See, e.g., U.S. Pat. No. 6,107,090.

An antibody or other specific-binding partner can be conjugated to a second molecule, such as a cytotoxic agent, and used for targeting the second molecule to a tissue-antigen positive cell (Vitetta, E. S. et al., 1993, Immunotoxin therapy, in DeVita, Jr., V. T. et al., eds, Cancer: Principles and Practice of Oncology, 4th ed., J. B. Lippincott Co., Philadelphia, 2624-2636). Examples of cytotoxic agents include, but are not limited to, antimetabolites, alkylating agents, anthracyclines, antibiotics, anti-mitotic agents, radioisotopes and

chemotherapeutic agents. Further examples of cytotoxic agents include, but are not limited to ricin, doxorubicin, daunorubicin, taxol, ethidium bromide, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicine, dihydroxy anthracin dione, actinomycin D, 1-dehydrotestosterone, diptheria toxin, Pseudomonas exotoxin (PE) A, PE40, abrin, elongation factor-2 and glucocorticoid. Techniques for conjugating therapeutic agents to antibodies are well.

In addition to immunotherapy, polynucleotides and polypeptides can be used as targets for non-immunotherapeutic applications, e.g., using compounds which interfere with function, expression (e.g., antisense as a therapeutic agent), assembly, etc. RNA interference can be used in vitro and in vivo to silence a gene when its expression contributes to a disease (but also for other purposes, e.g., to identify the gene's function to change a developmental pathway of a cell, etc.). See, e.g., Sharp and Zamore, *Science*, 287:2431-2433, 2001; Grishok et al., *Science*, 287:2494, 2001.

Delivery of therapeutic agents can be achieved according to any effective method, including, liposomes, viruses, plasmid vectors, bacterial delivery systems, orally, systemically, etc. Therapeutic agents of the present invention can be administered in any form by any effective route, including, e.g., oral, parenteral, enteral, intraperitoneal, topical, transdermal (e.g., using any standard patch), intravenously, ophthalmic, nasally, local, non-oral, such as aerosal, inhalation, subcutaneous, intramuscular, buccal, sublingual, rectal, vaginal, intra-arterial, and intrathecal, etc. They can be administered alone, or in combination with any ingredient(s), active or inactive.

In addition to therapeutics, *per se*, the present invention also relates to methods of treating a disease showing altered expression of a tissue selective gene, comprising, e.g., administering to a subject in need thereof a therapeutic agent which is effective for regulating expression of said gene and/or which is effective in treating said disease. The term "treating" is used conventionally, e.g., the management or care of a subject for the purpose of combating, alleviating, reducing, relieving, improving the condition of, etc., of a disease or disorder. By the phrase "altered expression," it is meant that the disease is associated with a mutation in the gene, or any modification to the gene (or corresponding product) which affects its normal function. Thus, expression refers to, e.g., transcription, translation, splicing, stability of the mRNA or protein product, activity of the gene product, differential

expression, etc.

Any agent which "treats" the disease can be used. Such an agent can be one which regulates the expression of a tissue selective gene. Expression refers to the same acts already mentioned, e.g. transcription, translation, splicing, stability of the mRNA or protein product, activity of the gene product, differential expression, etc. For instance, if the condition was a result of a complete deficiency of the gene product, administration of gene product to a patient would be said to treat the disease and regulate the gene's expression. Many other possible situations are possible, e.g., where the gene is aberrantly expressed, and the therapeutic agent regulates the aberrant expression by restoring its normal expression pattern.

Antisense

Antisense polynucleotide (e.g., RNA) can also be prepared from a polynucleotide according to the present invention. Antisense polynucleotide can be used in various ways, such as to regulate or modulate expression of the polypeptides they encode, e.g., inhibit their expression, for in situ hybridization, for therapeutic purposes, for making targeted mutations (in vivo, triplex, etc.) etc. For guidance on administering and designing anti-sense, see, e.g., U.S. Pat. Nos. 6,200,960, 6,200,807, 6,197,584, 6,190,869, 6,190,661, 6,187,587, 6,168,950, 6,153,595, 6,150,162, 6,133,246, 6,117,847, 6,096,722, 6,087,343, 6,040,296, 6,005,095, 5,998,383, 5,994,230, 5,891,725, 5,885,970, and 5,840,708. An antisense polynucleotides can be operably linked to an expression control sequence. A total length of about 35 bp can be used in cell culture with cationic liposomes to facilitate cellular uptake, but for *in vivo* use, preferably shorter oligonucleotides are administered, e.g. 25 nucleotides.

Antisense polynucleotides can comprise modified, nonnaturally-occurring nucleotides and linkages between the nucleotides (e.g., modification of the phosphate-sugar backbone; methyl phosphonate, phosphorothioate, or phosphorodithioate linkages; and 2'-O-methyl ribose sugar units), e.g., to enhance in vivo or in vitro stability, to confer nuclease resistance, to modulate uptake, to modulate cellular distribution and compartmentalization, etc. Any effective nucleotide or modification can be used, including those already mentioned, as known in the art, etc., e.g., disclosed in U.S. Pat. Nos. 6,133,438; 6,127,533; 6,124,445; 6,121,437; 5,218,103 (e.g., nucleoside thiophosphoramidites); 4,973,679; Sproat et al., "2'-O-Methyloligoribonucleotides: synthesis and applications," Oligonucleotides and Analogs A

Practical Approach, Eckstein (ed.), IRL Press, Oxford, 1991, 49-86; Iribarren et al., "2'O-Alkyl Oligoribonucleotides as Antisense Probes," Proc. Natl. Acad. Sci. USA, 1990, 87, 7747-7751; Cotton et al., "2'-O-methyl, 2'-O-ethyl oligoribonucleotides and phosphorothioate oligodeoxyribonucleotides as inhibitors of the in vitro U7 snRNP-dependent mRNA processing event," Nucl. Acids Res., 1991, 19, 2629-2635.

Arrays

The present invention also relates to an ordered array of polynucleotide probes and specific-binding partners (e.g., antibodies) for detecting the expression of tissue selective genes or polypeptides encoded thereby, in a sample, comprising, one or more polynucleotide probes or specific binding partners associated with a solid support or in separate receptacles, wherein each probe is specific for a tissue selective gene or a specific-binding partner which is specific for a polypeptide.

The phrase "ordered array" indicates that the probes are arranged in an identifiable or position-addressable pattern, e.g., such as the arrays disclosed in U.S. Pat. Nos. 6,156,501, 6,077,673, 6,054 ,270, 5,723,320, 5,700,637, WO09919711, WO00023803. The probes are associated with the solid support in any effective way. For instance, the probes can be bound to the solid support, either by polymerizing the probes on the substrate, or by attaching a probe to the substrate. Association can be, covalent, electrostatic, noncovalent, hydrophobic, hydrophilic, noncovalent, coordination, adsorbed, absorbed, polar, etc. When fibers or hollow filaments are utilized for the array, the probes can fill the hollow orifice, be absorbed into the solid filament, be attached to the surface of the orifice, etc. Probes can be of any effective size, sequence identity, composition, etc., as already discussed.

Transgenic animals

The present invention also relates to transgenic animals comprising tissue selective genes, and homologs thereof. (Methods of making transgenic animals, and associated recombinant technology, can be accomplished conventionally, e.g., as described in *Transgenic Animal Technology*, Pinkert et al., 2nd Edition, Academic Press, 2002.) Such genes, as discussed in more detail below, include, but are not limited to, functionally-disrupted genes, mutated genes, ectopically or selectively-expressed genes, inducible or

regulatable genes, etc. These transgenic animals can be produced according to any suitable technique or method, including homologous recombination, mutagenesis (e.g., ENU, Rathkolb et al., *Exp. Physiol.*, 85(6):635-644, 2000), and the tetracycline-regulated gene expression system (e.g., U.S. Pat. No. 6,242,667). The term "gene" as used herein includes any part of a gene, i.e., regulatory sequences, promoters, enhancers, exons, introns, coding sequences, etc. The nucleic acid present in the construct or transgene can be naturally-occurring wild-type, polymorphic, or mutated. Where the animal is a non-human animal, its homolog can be used instead. Transgenic animals can have structural and/or functional defects in any of the tissues described herein, e.g., pancreas, kidney, retina, and immune cells, as well as having or being susceptible to any of the associated disorders or diseases mentioned herein.

Along these lines, polynucleotides of the present invention can be used to create transgenic animals, e.g. a non-human animal, comprising at least one cell whose genome comprises a functional disruption of one or tissue selective genes, or homologs thereof (e.g., a mouse homolog when a mouse is used). By the phrases "functional disruption" or "functionally disrupted," it is meant that the gene does not express a biologically-active product. It can be substantially deficient in at least one functional activity coded for by the gene. Expression of a polypeptide can be substantially absent, i.e., essentially undetectable amounts are made. However, polypeptide can also be made, but which is deficient in activity, e.g., where only an amino-terminal portion of the gene product is produced.

The transgenic animal can comprise one or more cells. When substantially all its cells contain the engineered gene, it can be referred to as a transgenic animal "whose genome comprises" the engineered gene. This indicates that the endogenous gene loci of the animal has been modified and substantially all cells contain such modification.

Functional disruption of the gene can be accomplished in any effective way, including, e.g., introduction of a stop codon into any part of the coding sequence such that the resulting polypeptide is biologically inactive (e.g., because it lacks a catalytic domain, a ligand binding domain, etc.), introduction of a mutation into a promoter or other regulatory sequence that is effective to turn it off, or reduce transcription of the gene, insertion of an exogenous sequence into the gene which inactivates it (e.g., which disrupts the production of a biologically-active polypeptide or which disrupts the promoter or other transcriptional

machinery), deletion of sequences from the gene (or homolog thereof), etc. Examples of transgenic animals having functionally disrupted genes are well known, e.g., as described in U.S. Pat. Nos. 6,239,326, 6,225,525, 6,207,878, 6,194,633, 6,187,992, 6,180,849, 6,177,610, 6,100,445, 6,087,555, 6,080,910, 6,069,297, 6,060,642, 6,028,244, 6,013,858, 5,981,830, 5,866,760, 5,859,314, 5,850,004, 5,817,912, 5,789,654, 5,777,195, and 5,569,824. A transgenic animal which comprises the functional disruption can also be referred to as a "knock-out" animal, since the biological activity of its gene has been "knocked-out." Knock-outs can be homozygous or heterozygous.

For creating functionally disrupted genes, and other gene mutations, homologous recombination technology is of special interest since it allows specific regions of the genome to be targeted. Using homologous recombination methods, genes can be specifically-inactivated, specific mutations can be introduced, and exogenous sequences can be introduced at specific sites. These methods are well known in the art, e.g., as described in the patents above. See, also, Robertson, *Biol. Reproduc.*, 44(2):238-245, 1991. Generally, the genetic engineering is performed in an embryonic stem (ES) cell, or other pluripotent cell line (e.g., adult stem cells, EG cells), and that genetically-modified cell (or nucleus) is used to create a whole organism. Nuclear transfer can be used in combination with homologous recombination technologies. For example, a gene locus can be disrupted in mouse ES cells using a positive-negative selection method (e.g., Mansour et al., *Nature*, 336:348-352, 1988). In this method, a targeting vector can be constructed which comprises a part of the gene to be targeted. A selectable marker, such as neomycin resistance genes, can be inserted into a an exon present in the targeting vector, disrupting it. When the vector recombines with the ES cell genome, it disrupts the function of the gene. The presence in the cell of the vector can be determined by expression of neomycin resistance. See, e.g., U.S. Pat. No. 6,239,326. Cells having at least one functionally disrupted gene can be used to make chimeric and germline animals, e.g., animals having somatic and/or germ cells comprising the engineered gene. Homozygous knock-out animals can be obtained from breeding heterozygous knock-out animals. See, e.g., U.S. Pat. No. 6,225,525.

The present invention also relates to non-human; transgenic animal whose genome comprises recombinant tissue selective nuccleic acid (and homologs thereof) operatively linked to an expression control sequence effective to express said coding sequence in a target

tissue. Such a transgenic animal can also be referred to as a "knock-in" animal since an exogenous gene has been introduced, stably, into its genome. "Operable linkage" has the meaning used through the specification, i.e., placed in a functional relationship with another nucleic acid. When a gene is operably linked to an expression control sequence, as explained above, it indicates that the gene (e.g., coding sequence) is joined to the expression control sequence (e.g., promoter) in such a way that facilitates transcription and translation of the coding sequence. As described above, the phrase "genome" indicates that the genome of the cell has been modified. In this case, the recombinant gene has been stably integrated into the genome of the animal. The nucleic acid (e.g., a coding sequence) in operable linkage with the expression control sequence can also be referred to as a construct or transgene.

Any expression control sequence can be used depending on the purpose. For instance, if selective expression is desired, then expression control sequences which limit its expression can be selected. These include, e.g., tissue or cell-specific promoters, introns, enhancers, etc. For various methods of cell and tissue-specific expression, see, e.g., U.S. Pat. Nos. 6,215,040, 6,210,736, and 6,153,427. These also include the endogenous promoter, i.e., the coding sequence can be operably linked to its own promoter. Inducible and regulatable promoters can also be utilized.

The present invention also relates to a transgenic animal which contains a functionally disrupted and a transgene stably integrated into the animals genome. Such an animal can be constructed using combinations any of the above- and below-mentioned methods. Such animals have any of the aforementioned uses, including permitting the knock-out of the normal gene and its replacement with a mutated gene. Such a transgene can be integrated at the endogenous gene locus so that the functional disruption and "knock-in" are carried out in the same step.

In addition to the methods mentioned above, transgenic animals can be prepared according to known methods, including, e.g., by pronuclear injection of recombinant genes into pronuclei of 1-cell embryos, incorporating an artificial yeast chromosome into embryonic stem cells; gene targeting methods, embryonic stem cell methodology, cloning methods, nuclear transfer methods. See, also, e.g., U.S. Patent Nos. 4,736,866; 4,873,191; 4,873,316; 5,082,779; 5,304,489; 5,174,986; 5,175,384; 5,175,385; 5,221,778; Gordon et al., Proc. Natl. Acad. Sci., 77:7380-7384, 1980; Palmiter et al., Cell, 41:343-345, 1985; Palmiter

et al., Ann. Rev. Genet., 20:465-499, 1986; Askew et al., Mol. Cell. Bio., 13:4115-4124, 1993; Games et al. Nature, 373:523-527, 1995; Valancius and Smithies, Mol. Cell. Bio., 11:1402-1408, 1991; Stacey et al., Mol. Cell. Bio., 14:1009-1016, 1994; Hasty et al., Nature, 350:243-246, 1995; Rubinstein et al., Nucl. Acid Res., 21:2613-2617,1993; Cibelli et al., Science, 280:1256-1258, 1998. For guidance on recombinase excision systems, see, e.g., U.S. Pat. Nos. 5,626,159, 5,527,695, and 5,434,066. See also, Orban, P.C., et al., "Tissue- and Site-Specific DNA Recombination in Transgenic Mice," Proc. Natl. Acad. Sci. USA, 89:6861-6865 (1992); O'Gorman, S., et al., "Recombinase-Mediated Gene Activation and Site-Specific Integration in Mammalian Cells," Science, 251:1351-1355 (1991); Sauer, B., et al., "Cre-stimulated recombination at loxP-Containing DNA sequences placed into the mammalian genome," Polynucleotides Research, 17(1):147-161 (1989); Gagneten, S. et al. (1997) Nucl. Acids Res. 25:3326-3331; Xiao and Weaver (1997) Nucl. Acids Res. 25:2985-2991; Agah, R. et al. (1997) J. Clin. Invest. 100:169-179; Barlow, C. et al. (1997) Nucl. Acids Res. 25:2543-2545; Araki, K. et al. (1997) Nucl. Acids Res. 25:868-872; Mortensen, R. N. et al. (1992) Mol. Cell. Biol. 12:2391-2395 (G418 escalation method); Lakhlani, P. P. et al. (1997) Proc. Natl. Acad. Sci. USA 94:9950-9955 ("hit and run"); Westphal and Leder (1997) Curr. Biol. 7:530-533 (transposon-generated "knock-out" and "knock-in"); Templeton, N. S. et al. (1997) Gene Ther. 4:700-709 (methods for efficient gene targeting, allowing for a high frequency of homologous recombination events, e.g., without selectable markers); PCT International Publication WO 93/22443 (functionally-disrupted).

A polynucleotide according to the present invention can be introduced into any non-human animal, including a non-human mammal, mouse (Hogan et al., Manipulating the Mouse Embryo: A Laboratory Manual, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, 1986), pig (Hammer et al., Nature, 315:343-345, 1985), sheep (Hammer et al., Nature, 315:343-345, 1985), cattle, rat, or primate. See also, e.g., Church, 1987, Trends in Biotech. 5:13-19; Clark et al., Trends in Biotech. 5:20-24, 1987); and DePamphilis et al., BioTechniques, 6:662-680, 1988. Transgenic animals can be produced by the methods described in U.S. Pat. No. 5,994,618, and utilized for any of the utilities described therein.

Database

The present invention also relates to electronic forms of polynucleotides,

polypeptides, etc., of the present invention, including computer-readable medium (e.g., magnetic, optical, etc., stored in any suitable format, such as flat files or hierarchical files) which comprise such sequences, or fragments thereof, e-commerce-related means, etc. Along these lines, the present invention relates to methods of retrieving nucleic acid and/or polypeptide sequences from a computer-readable medium, comprising, one or more of the following steps in any effective order, e.g., selecting a cell or gene expression profile, e.g., a profile that specifies that said gene is differentially expressed in a tissue as described herein, and retrieving said differentially expressed nucleic acid or polypeptide.

A "gene expression profile" means the list of tissues, cells, etc., in which a defined gene is expressed (i.e, transcribed and/or translated). A "cell expression profile" means the genes which are expressed in the particular cell type. The profile can be a list of the tissues in which the gene is expressed, but can include additional information as well, including level of expression (e.g., a quantity as compared or normalized to a control gene), and information on temporal (e.g., at what point in the cell-cycle or developmental program) and spatial expression. By the phrase "selecting a gene or cell expression profile," it is meant that a user decides what type of gene or cell expression pattern he is interested in retrieving, e.g., he may require that the gene is differentially expressed in a tissue, or he may require that the gene is not expressed in blood, but must be expressed in pancreas. Any pattern of expression preferences may be selected. The selecting can be performed by any effective method. In general, "selecting" refers to the process in which a user forms a query that is used to search a database of gene expression profiles. The step of retrieving involves searching for results in a database that correspond to the query set forth in the selecting step. Any suitable algorithm can be utilized to perform the search query, including algorithms that look for matches, or that perform optimization between query and data. The database is information that has been stored in an appropriate storage medium, having a suitable computer-readable format. Once results are retrieved, they can be displayed in any suitable format, such as HTML.

For instance, the user may be interested in identifying genes that are differentially expressed in a pancreas or kidney. He may not care whether small amounts of expression occur in other tissues, as long as such genes are not expressed in peripheral blood lymphocytes. A query is formed by the user to retrieve the set of genes from the database

having the desired gene or cell expression profile. Once the query is inputted into the system, a search algorithm is used to interrogate the database, and retrieve results.

Advertising, licensing, etc., methods

The present invention also relates to methods of advertising, licensing, selling, purchasing, brokering, etc., genes, polynucleotides, specific-binding partners, antibodies, etc., of the present invention. Methods can comprises, e.g., displaying tissue selective polynucleotide or polypeptide sequences, or antibody specific thereto, in a printed or computer-readable medium (e.g., on the Web or Internet), accepting an offer to purchase said gene, polypeptide, or antibody.

Other

A polynucleotide, probe, polypeptide, antibody, specific-binding partner, etc., according to the present invention can be isolated. The term "isolated" means that the material is in a form in which it is not found in its original environment or in nature, e.g., more concentrated, more purified, separated from component, etc. An isolated polynucleotide includes, e.g., a polynucleotide having the sequenced separated from the chromosomal DNA found in a living animal, e.g., as the complete gene, a transcript, or a cDNA. This polynucleotide can be part of a vector or inserted into a chromosome (by specific gene-targeting or by random integration at a position other than its normal position) and still be isolated in that it is not in a form that is found in its natural environment. A polynucleotide, polypeptide, etc., of the present invention can also be substantially purified. By substantially purified, it is meant that polynucleotide or polypeptide is separated and is essentially free from other polynucleotides or polypeptides, i.e., the polynucleotide or polypeptide is the primary and active constituent. A polynucleotide can also be a recombinant molecule. By "recombinant," it is meant that the polynucleotide is an arrangement or form which does not occur in nature. For instance, a recombinant molecule comprising a promoter sequence would not encompass the naturally-occurring gene, but would include the promoter operably linked to a coding sequence not associated with it in nature, e.g., a reporter gene, or a truncation of the normal coding sequence.

The term "marker" is used herein to indicate a means for detecting or labeling a target. A marker can be a polynucleotide (usually referred to as a "probe"), polypeptide (e.g., an antibody conjugated to a detectable label), PNA, or any effective material.

The topic headings set forth above are meant as guidance where certain information can be found in the application, but are not intended to be the only source in the application where information on such topic can be found. Reference materials

For other aspects of the polynucleotides, reference is made to standard textbooks of molecular biology. See, e.g., Hames et al., Polynucleotide Hybridization, IL Press, 1985; Davis et al., Basic Methods in Molecular Biology, Elsevir Sciences Publishing, Inc., New York, 1986; Sambrook et al., Molecular Cloning, CSH Press, 1989; Howe, Gene Cloning and Manipulation, Cambridge University Press, 1995; Ausubel et al., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., 1994-1998.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. The entire disclosure of all applications, patents and publications, cited above and in the figures are hereby incorporated by reference in their entirety, including U.S. Application Serial Nos. 60/372,669 April 16, 2003, 60/374,823 filed April 24, 2002, 60/376,558 filed May 1, 2002, 60/381,366 filed May 20, 2002, 60/403,648 filed August 16, 2002, 60/411,882 filed September 20, 2002, and 60/424,336 filed November 7, 2002.

TABLE 1

Clone ID (gene code)	ACCN	Predominant sites of expression	Other expression sites	Cytogenetic locus
TMD0024	XM_060945	thymus	none	1q22
TMD1779	XM_060946	thymus and PBL	none	1q22
TMD0884	XM_060947	thymus	skin and ovary	1q22
TMD0025	XM_060948	thymus	none	1q22
TMD1780	XM_089422	thymus	none	1q22
TMD1781	XM_089421	PBL	thymus	1q22
TMD0304	XM_060956	bone marrow and muscle	testis	1q22
TMD0888	XM_060957	bone marrow	lung, muscle and testis	1q22
TMD0890	XM_060959	bone marrow	lung and PBL	1q22

TABLE 2

Clone ID (gene code)	ACCN	Protein seq length	Domain Description
TMD1779	XM_060946	264	Transmembrane domain: 26 - 48 Transmembrane domain: 55 - 77 Transmembrane domain: 92 - 114 Transmembrane domain: 134 - 156 Transmembrane domain: 197 - 219
TMD0024	XM_060945	268	Transmembrane domain: 16 - 38 Transmembrane domain: 53 - 75 Transmembrane domain: 96 - 118 Transmembrane domain: 156 - 178 Transmembrane domain: 191 - 213 Transmembrane domain: 228 - 246
TMD0025	XM_060948	313	Transmembrane domain: 29 - 51 Transmembrane domain: 58 - 77 Transmembrane domain: 92 - 114 Transmembrane domain: 135 -157 Transmembrane domain: 197 - 219 Transmembrane domain: 240 - 262 Transmembrane domain: 272 - 294
TMD0304	XM_060956	319	Transmembrane domain: 28 - 50 Transmembrane domain: 63 - 82 Transmembrane domain: 102 - 124 Transmembrane domain: 144 - 166 Transmembrane domain: 205 - 227 Transmembrane domain: 240 - 262 Transmembrane domain: 272 - 294
TMD0884	XM_060947	299	Transmembrane domain: 20 - 42 Transmembrane domain: 54 - 76 Transmembrane domain: 91 - 113 Transmembrane domain: 126 - 148

			Transmembrane domain: 183 - 205 Transmembrane domain: 226 - 248 Transmembrane domain: 258 - 277
TMD0888	XM_060957	312	Transmembrane domain: 25 - 47 Transmembrane domain: 59 - 78 Transmembrane domain: 98 - 120 Transmembrane domain: 141 - 163 Transmembrane domain: 207 - 229 Transmembrane domain: 241 - 260 Transmembrane domain: 270 - 292
TMD0890	XM_060959	280	Transmembrane domain: 26 - 48 Transmembrane domain: 122 - 144 Transmembrane domain: 180 - 202 Transmembrane domain: 215 - 237 Transmembrane domain: 252 - 269
TMD1780	XM_089422	491	Transmembrane domain: 20 - 42 Transmembrane domain: 54 - 76 Transmembrane domain: 91 - 113 Transmembrane domain: 137 - 159 Transmembrane domain: 190 - 212 Transmembrane domain: 231 - 253 Transmembrane domain: 266 - 283 Transmembrane domain: 304 - 326 Transmembrane domain: 336 - 358 Transmembrane domain: 379 - 401 Transmembrane domain: 437 - 459
TMD1781	XM_089421	91	Transmembrane domain: 63 - 85

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	TMD0024 XM_060945	TMD1779 XM_060946	TMD0884 XM_060947	TMD0025 XM_060948	TMD1780 XM_089422	TMD1781 XM_089421	TMD0304 XM_060956	TMD0888 XM_060957
TMD0024 XM_060945								
TMD1779 XM_060946	no significant similarity							
TMD0884 XM_060947	74%(371nt)	no significant similarity						
TMD0025 XM_060948	71%(222nt) 80%(73nt)	90%(605nt)	83%(54nt)					
TMD1780 XM_089422	81%(114nt) 74%(186nt) 79%(113nt) 77%(99nt)	83%(71nt)	78%(90nt)	80%(84nt)				
TMD1781 XM_089421	91%(35nt) 77%(80nt)	no significant similarity	no significant similarity	no significant similarity	77%(179nt) 82%(46nt)			
TMD0304 XM_060956	no significant similarity	no significant similarity	no significant similarity	no significant similarity	84%(39nt)	no significant similarity		
TMD0888 XM_060957	no significant similarity	no significant similarity	no significant similarity	84% (38nt)	no significant similarity	no significant similarity	73%(241nt)	
TMD0890 XM_060959	no significant similarity	no significant similarity	no significant similarity	no significant similarity	no significant similarity	no significant similarity	no significant similarity	84%(39nt)

TABLE 3

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	TMD0024 XP_060945	TMD1779 XP_060946	TMD0884 XP_060947	TMD0025 XP_060948	TMD1780 XP_089422	TMD1781 XP_089421	TMD0304 XP_060956	TMD0888 XP_060957
TMD0024 XP_060945								
TMD1779 XP_060946	47%(200aa)							
TMD0884 XP_060947	62%(171aa)	36%(92aa)						
TMD0025 XP_060948	53%(252aa)	73%(233aa)	46%(166aa)					
TMD1780 XP_089422	59%(261aa) 59%(181aa)	46%(227aa) 46%(169aa)	55%(165aa) 47%(111aa)	52%(300aa)				
TMD1781 XP_089421	40%(94aa)	35%(82aa)	52%(40aa)	37%(94aa)	51%(93aa) 49%(77aa)			
TMD0304 XP_060956	40%(257aa)	37%(229aa)	36% (163aa)	39%(299aa)	39%(300aa)	34%(89aa)		
TMD0888 XP_060957	49%(251aa)	37%(239aa)	41%(157aa)	40% (305aa)	45%(304aa) 43%(189aa)	41%(82aa)	50%(301aa)	
TMD0890 XP_060959	41%(196)	32%(132aa)	32%(156aa)	36%(179aa)	42%(200aa)	38%(72aa)	36%(196aa)	46%(196aa)

TABLE 4

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TABLE 5

CLONE ID	F-OLIGO	R-OLIGO	PROMOTER
TMD1779 (SEQ ID NO 1-2)	GGTCAATGAGACTGTGG TGAGAGAGGTCATCT (SEQ ID NO 3)	CTATCACTCCCAGTGTGGAA GGAAACTGAAG (SEQ ID NO 4)	CTCTTTCAGATTTAAATGGGCCAGACTTAGTTTTATGTGGTGCAGACATT (SEQ ID NO 5)
TMD0024 (SEQ ID NO 6-7)	CCACCTGCTCTCAGACA CCAAGACC (SEQ ID NO 8)	GGCACCATAATTACCAGGAT GCTGAGG (SEQ ID NO 9)	GAGTGCCAAATATATAAAGAGGTATGTTCAATGCAACATGTTAAATGCAA (SEQ ID NO 10) ACTCCTTAGATAAAAAAGGGCAGATTTATTAAAGAACCCTGATTTAATCA (SEQ ID NO 11)
TMD0025 (SEQ ID NO 12-13)	CCTGTTCACTCTGGGCA CCAATGC (SEQ ID NO 14)	CTGGTTGGAGGAGTGGAAG GGCAG (SEQ ID NO 15)	TAATACTATGTAAAAATCCACTGGACTAGAATCAGCTGTCCTCATGTGCC (SEQ ID NO 19) TACCTTTCTGTATATAAAAACATATAACTAATACACACACACTCATACAC (SEQ ID NO 16) CTTCAGAAGTATATAAATGAAGACTGGATACCAGCAAGACATACTGGATG (SEQ ID NO 17) CCCTTGGAGATATAAAAAGTTCCCAGTAAATAGATGTGTGCTCACATCTT (SEQ ID NO 18)
TMD0304 (SEQ ID NO 20-21)	CTCTATGTTCCCGCATGC GCACAG (SEQ ID NO 22)	GCAAGGTGGAAATCCATGCA ATCTCAG (SEQ ID NO 23)	AGACAGACGTTAAAAAATGACCAAACCTACAGAAAATATTTCCAGATAAT (SEQ ID NO 24)
TMD0884 (SEQ ID NO 25-26)	TGTCAATATCCTGGTGTT CAGTGTGCTCC (SEQ ID NO 27)	CATCTACCCAGAACCTTTCT CAGAGCCATC (SEQ ID NO 28)	GTCACTGGTGTATAAGCACGCAGTGCAAAGGAAATATTAAAACTAGAACC (SEQ ID NO 29) TTTCTTCATTTATAACATGAGGGGGCTTGGCTAGATATTTAACAGCCTGC (SEQ ID NO 30) GCTAGATATTTAACAGCCTGCCTGTATTGACCACTTATGCATCAGGAAAT (SEQ ID NO 31) ATTTGAGTTATGTATATGAGAGACTGGGTACATCACTTTTTACTTGTTTT (SEQ ID NO 32)
TMD0888 (SEQ ID NO 33-34)	GGAACTGGAGCCAGGTA GCAGAATTCATC (SEQ ID NO 35)	GGAGCAGAGGATCAGCAGG AAGGTG (SEQ ID NO 36)	ACACTGCAGTTATATAGGGTGGCCCAGGTAGTTGAGCTGGTGAAATTTGA (SEQ ID NO 37) GCACTGTGACATTAAAAGGATGGGGCATGGAGGAGAAACTAAAGTTGGAG (SEQ ID NO 38) ATTCAAATTATATATATTTGGTCCAGTACGGTATCAATATATTATCAGTA (SEQ ID NO 39)
TMD0890 (SEQ ID NO 40-41)	TCACCACCACTGGGACC CTACAACCT (SEQ ID NO 42)	GGCCACACCAATCACTGTGC CAT (SEQ ID NO 43)	CAATCTGTTATTTATACGGCCTCTACATCCATCCAGTACCTGCTTATGTA (SEQ ID NO 44) GTTCTCTTTTTATAAAAGGCTATGTGGGACTTGCAAAACTTCTAGTGGCC (SEQ ID NO 45) GAACATGAAATATAAGTAGGGGAGTATCTTGGGGTAGAAAGGATGCCGAG (SEQ ID NO 46)
TMD1780 (SEQ ID NO 47-48)	CTCTGAAATCTTCTACAC AACTGTTATTCTGCCCA (SEQ ID NO 49)	ATGAGATGGGAAGCACAGGT GGAGAAG (SEQ ID NO 50)	ATCAATATTGTTAAAATGGCCGTACTGTCAAAAGCAATTTACAGATTCAA (SEQ ID NO 51) ATATGAAACCAAAAAAGCCCTCAAATAGCCCAAGTAACCCTAAAGAAAAA (SEQ ID NO 52) CGCCCTATTCAATAAATGGTGTGGGAATAGCTGGCTAGCCATCTGCAGAA (SEQ ID NO 53) CATAAGGGTTCTTAAAATTGGGAGAGAGAATCAGAAAGTCAGAGAAAGAG (SEQ ID NO 54)
TMD1781 (SEQ ID NO 55-56)	ATGACAGTTTATGATTCC TATGTTGCCATCTGC (SEQ ID NO 57)	TCAGGATGGTGTGAACAATG AAGCCATAG (SEQ ID NO 58)	TTCCCTATTTAATAAATGGTGCTGGGAAAACTGGCTAGCCATATGTAGAA (SEQ ID NO 59) AACAACCCCATCAAAAAGTGGGCCAAAGATATGAACAGACACTTCTCAAA (SEQ ID NO 60) AATGGCGATCATTAAAAAGTCAGGAAACAACAGGTGCTGGAGAGGATGTG (SEQ ID NO 61) CCCAGAGGATTATAAATCATGCTGCTGTAAAGACACATGCCCACGTATGT (SEQ ID NO 62)

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TABLE 6

SEQ ID NO	GENE NUMBER	GENBANK IDENTIFIER	PREDOMINANT SITES OF EXPRESSION	PROMOTER (SEQ ID NO)	PRIMER (FOR, REV) (SEQ ID NO)
63,64	TMD0785	XM_060310	kidney	65-68	69,70

TABLE 7

	XM_062147	XM_061676
outside	1-27	1-28
TM (1)	28-50	29-51
inside	51-61	52-62
TM (2)	62-84	63-85
outside	85-98	86-99
TM (3)	99-121	100-122
inside	122-140	123-133
TM (4)	141-163	134-156
outside	164-203	157-201
TM (5)	204-226	202-224
inside	227-237	225-236
TM (6)	238-260	237-259
outside	261-274	260-273
TM (7)	275-293	274-296
inside	294-313	297-314

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Clone ID (gene code)	ACCN	Gene Name/Description	Predominant Sites of expression	Other expression sites
TMD0049	XM_057351	Homo sapiens similar to organic anion transpoter 4 like protein (LOC116085) mRNA	kidney	none
TMD0190	XM_087157	Homo sapiens similar to sodium-coupled ascorbic acid transporter 2(LOC151295), mRNA.	kidney	colon and liver
TMD0242	XM_088369	Homo sapiens similar to unnamed protein product (LOC157724) mRNA	kidney	none
TMD0335	XM_089960	Homo sapiens similar to sodium iodide symporter (LOC159963) mRNA	kidney	adrenal gland, heart, intestine(small), liver, muscle, testis
TMD0371 (new)	XM_089732	Homo sapiens similar to CG8271 gene product (LOC196023), mRNA.	kidney	pancreas and testis
TMD0374 (new)	XM_085595	Homo sapiens similar to unnamed protein product (LOC146802) mRNA	kidney	brain, muscle, ovary, skin, testis
TMD0469	XM_038736	Homo sapiens solute carrier family 4 sodium bicarbonate cotransporter member 9 (SLC4A9) mRNA	kidney	none
TMD0719	XM_059548	Homo sapiens hypothetical gene supported by XM_059548 (LOC131920) mRNA	kidney	none
TMD0731	XM_059703	Homo sapiens similar to putative (H. sapiens) (LOC134288) mRNA	kidney	adrenal gland, muscle, thyroid
TMD0785	XM_060310	Homo sapiens similar to olfactory receptor MOR275-2 (LOC127069), mRNA	kidney	none
TMD0841	XM_060623	Homo sapiens similar to KIAA0711 gene product (H. sapiens) (LOC127707) mRNA	kidney	lung
TMD1114	NM_019841	Homo sapiens transient receptor potential cation channel subfamily V member 5 (TRPV5) mRNA	kidney	none
TMD1148	XM_087108	Homo sapiens similar to calcium channel voltage-dependent gamma subunit 6 (LOC151151) mRNA	kidney	none

TABLE 8

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TABLE 9

Gene Code	SEQ ID NO	Protein seq length(aa)	domain description
TMD0049	2	332	Sugar (and other) transporter: 2 - 302
			Transmembrane domain: 12 - 34
			Transmembrane domain: 39 - 58
			Transmembrane domain: 131 - 153
			Transmembrane domain: 157 - 179
			Transmembrane domain: 186 - 205
			Transmembrane domain: 215 - 237
TMD0190	4	243	Permease family: 91 - 224
TMD0242	6	470	AA-permease: 27 - 356
			Transmembrane domain: 13 - 35
			Transmembrane domain: 50 - 72
			Transmembrane domain: 93 - 115
			Transmembrane domain: 137 - 154
			Transmembrane domain: 161 - 183
			Transmembrane domain: 207 - 229
			Transmembrane domain: 242 - 264
			Transmembrane domain: 286 - 308
			Transmembrane domain: 335 - 357
			Transmembrane domain: 362 - 379
			Transmembrane domain: 392 - 414
			Transmembrane domain: 420 - 442

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TMD0335	8	178	Sodium solute symporter family: 41 - 172
TMD0371	10	516	Transmembrane domain: 45 - 67
			Transmembrane domain: 87 - 109
			Transmembrane domain: 116 - 138
			Transmembrane domain: 143 - 165
			Transmembrane domain: 174 - 196
			Transmembrane domain: 201 - 223
			Transmembrane domain: 283 - 305
			Transmembrane domain: 320 - 339
			Transmembrane domain: 351 - 370
			Transmembrane domain: 375 - 397
			Transmembrane domain: 404 - 426
			Transmembrane domain: 441 - 463
TMD0374	12	566	Transmembrane domain: 31 - 53
			Transmembrane domain: 68 - 90
			Transmembrane domain: 116 - 138
			Transmembrane domain: 153 - 171
			Transmembrane domain: 184 - 206
			Transmembrane domain: 211 - 233
			Transmembrane domain: 254 - 273
			Transmembrane domain: 288 - 310
			Transmembrane domain: 331 - 353
			Transmembrane domain: 373 - 395
			Transmembrane domain: 404 - 426
			Transmembrane domain: 431 - 453
			Transmembrane domain: 542 - 564

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TMD0469	14	983	HCO3- transporter family: 108 - 891
			Transmembrane domain: 413 - 435
			Transmembrane domain: 447 - 469
			Transmembrane domain: 498 - 520
			Transmembrane domain: 532 - 554
			Transmembrane domain: 623 - 645
			Transmembrane domain: 665 - 684
			Transmembrane domain: 712 - 731
			Transmembrane domain: 751 - 773
			Transmembrane domain: 813 - 832
			Transmembrane domain: 839 - 858
			Transmembrane domain: 897 - 919
TMD0719	16	146	Transmembrane domain: 7 - 29
			Transmembrane domain: 49 - 71
TMD0731	18	218	Transmembrane domain: 38 - 60
			Transmembrane domain: 70 - 92
TMD0785	20	312	7 transmembrane receptor (rhodopsin family): 58 - 290
			Transmembrane domain: 29 - 51
			Transmembrane domain: 61 - 83
			Transmembrane domain: 140 - 162
			Transmembrane domain: 197 - 219
			Transmembrane domain: 240 - 262
			Transmembrane domain: 272 - 294
TMD0841	22	1161	Kelch motif: 850 - 895
			Kelch motif: 897 - 938

TMD1114	24	729	Transmembrane domain: 327 - 349
			Transmembrane domain: 383 - 405
			Transmembrane domain: 420 - 438
			Transmembrane domain: 451 - 473
			Transmembrane domain: 493 - 512
			Transmembrane domain: 519 - 541
			Transmembrane domain: 554 - 576
TMD1148	26	103	Transmembrane domain: 7 - 24
			Transmembrane domain: 39 - 61
			Transmembrane domain: 68 - 90

OCID: <WO_____03089583A2_I_>

DOCID: <WO 03089583A2_1 >

Clone ID (gene code)	ACCN	Cytogenetic locus	disease linkage
TMD0049	XM_057351	11q12.1	osteoporosis-pseudoglioma syndrome; spastic paraplegia 1 7
TMD0190	XM_087157	2q36.2	none
TMD0242	XM_088369	8q21.2	none
TMD0335	XM_089960	11p14.2	none
TMD0371A	XM_089732	10q23.33	epilepsy, partial, with auditory features; spastic paraplegia 9, autosomal dominant
TMD0374	XM_085595	17p11.2	smith-magenis syndrome
TMD0469	XM_038736	5q31	paget disease of bone 4
TMD0719	XM_059548	3q29	none
TMD0731	XM_059703	5q13.2	spastic paraplegia 11, autosomal recessive; corpus callosum, agenesis of, with neuronopathy
TMD0785	XM_060310	1q44-tel	familial cold urticaria (FCU); Muckle-Wells syndrome (MWS); prostate cancer susceptibility
TMD0841	XM_060623	1p36.13	breast cancer, ductal, 2; prostate cancer/brain cancer susceptibility; melanoma, cutaneous
TMD1114	NM_019841	7q35	glaucoma 1, open angle, f
TMD1148	XM_087108	2q14.1	motor neuronopathy, distal hereditary, with vocal cord paralysis; cardiomyopathy, dilated, 1h

TABLE 10

WO 03/089583 PCT/US03/11497

CODE (SEQ ID NO)	OLIGOS (SEQ ID NO)	PROMOTERS (SEQ ID NO)
TMD0049 (78,79)	GCGCTTCCGGACCTGTATCTCCAC (104) CAAGCTCTGGGTCTCGGGCAGAAG (105)	AAAGAGCCTCTAAAGAAGGGTTCCAGACTACCAGGAGCTCACTGGAAATA (106)
TMD0190 (80,81)	ACCATCCTGCAAACTTGGATGGGC (107) AAGGAGCCGGAAGACAGGGAGAGG (108)	GCTTTATGTATATGAAAACCCTGTTTATCTGAGCCTAGAACTGTCTTTGC (109) AGTGATAGTTTTAAATGGGAGGGAATAAAGTCTGCAAAATTTCCCCATAT (110)
TMD0242 (82,83)	GAGTCTCCCTGTGCGTTTGGGCTG (111) AAGTGTAAAGCATGCCCCGCCTGA (112)	AGTCCCAGCTTAAAAAAAGAGACAGACAGACAGAGAGAGAGAGAGACAGAG (113) TTAGTGATTTAAAAAAATGTGAAGAAGAGAGAGTCAAGGCAGTAAAAGGA (114)
TMD0335 (84,85)	GTTCGCTATGCTGCCACGGTCATC (115) AGTCCTGGCAGTCCTGGCATTGTG (116)	GATACAAATAATTAAAAAGCCCAGGTTAAGGTAAATATATTAAAGACCAAG (117) ATCTCACGAATTAAAAAATGCTGAGGTGGTAAATTGTTATCAATTCTATGT (118)
TMD0371 (86,87)	CAGGATTACGCACAAACGGCATGG (119) TGGGAGGCAGAGATAGCAGAGCCC (120)	CTAGACTATTTAAAAAAACCCCTGGCTTGCACAGTGGCTCAAGCCTGTAA (121)
TMD0374 (88,89)	CTGGTCCTGGGCACCCTGATAAGC (122) CCCAGGTCTGGTTGCAGTGCTCTC (123)	AGCTGTCCTCATTAAAAGTGACCTGGAGTGAGATGGATTCTTCTGCCTAT (124) CCAATTCTTCTGAAAAACGGGAGTCACTGTGGGCACCATCACGCCCGGGT (125)
TMD0469 (90,91)	CTGAGGTGTCCCTCCCAAGCAGGT (126) TACGGCCGAGAAGCACTGGAGATG (127)	TAAACAAATACATAAATGAGGCAGTTACTAGTAGTGGTAACTGCTAGGAA (128) ACTAAAAAATATAAAAAATCAGCCAGGCCTGGTGGCACATGTCTGTAATCTC (129) GGGATGCATTATAAATGCAACCAGCCAGAGGGCCCCTGGCTTCAGAACCT (130)
TMD0719 (92,93)	GTCACCTCAGCGATCTCAACGATAGGG (131) TGGAGCAGGAACAGGATATAGGTCAGGG (132)	ATATACCTTGTTTAAAAGAGGGGTATTATCACAATAAAACAAGGAAAGCT (133) ACCCCTACTTTTAAAGGCCTTGACAAACAGTGCTAAAGTTCTCACCTTAA (134)
TMD0731 (94,95)	GGGTGGGAAGGAAGCAGGGAAGAG (135) CCAGCTAGTTCATGCTTGGCGCAG (136)	TTATTGGGCATAAAAATATGAAGAGAGGTCCCAGAGAGTCCCTAGGTTCT (137)
TMD0785 (96,97)	CTGTTGGGAATCTTCAGCCAGATCTCACAC (138) ATGGAGGTTTCTGCACGCTCAGCA (139)	AAGCAATTTGTTAAAAACTGGCATTACTTTACTCTTATGCTTTCTGTGTC (140) ACTTTAATTTTATAAAGAAGGTTCACATCAAGAAATTCCAAGTGAGGTTC (141)
TMD0841 (98,99)	GGGCCACTTCCACAGACAGGAAGC (142) TGGCCTGAGAGGTAGATTCCACATAGTAGTCGT (143)	AAGGCTTCTTCAAAAAAAGCGGGCTTGTTCTGGGCCAGAAAATCAGAGTG (144)
TMD1114 (100,101)	CTCCTTTCTGGTCAGAGAACAAGACTGGGAC (145) GTGATGTCTCGAGAATGAGTGCGGTTG (146)	CAGCGAGGCAGAAAAATGTCCCACAAGTTGAGCCCTCCCCACTCCCAGTG (147) TAATATAAAATATATAAAATAGTGCAACATTACTTATTCCTCCTGGTGTT (148)
TMD1148 (102,103)	GCAGATGACCCGACCTGACTGTTCTTC (149) TGGCTGTGCAGCTAGCTCAGGTACCAG (150)	GCCAGAGAGTTTAAATGAAGCCCTACTTTGGGGCAGGAGCGGGAGGAAAC (151)

TABLE 11

SEQ ID NO	GENE NUMBER	GENBANK IDENTIFIER	PREDOMINANT SITES OF EXPRESSION	OTHER SITES OF EXPRESSION	PROMOTER (SEQ ID NO)	PRIMER (FOR, REV) (SEQ ID NO)
152, 153	TMD0986	XM_061779	pancreas	low levels in testis	156-161	154,155
162, 163	TMD0987	XM_061780	pancreas	low levels in testis	166	164,165
167, 168	TMD0353	XM_061781	pancreas			169,170
171, 172	TMD0989	XM_061784	pancreas			173,174
175, 176	TMD058	XM_061785	pancreas	low levels in testis	179,180	177,178

TABLE 12

DOCID: <WO_____03089583A2_1>

DOCID: <WO_____030858342 1_>

	XM_061779	XM_061780	XM_061781	XM_061784	XM_061785
outside	1-23	1-25	1-22		1-24
TM (1)	24-46	26-48	23-45		25-47
inside	47-58	49-60	46-65		48-59
TM (2)	59-78	61-83	66-88		60-82
outside	79-97	84-97	89-97		83-96
TM (3)	98-120	98-120	98-120		97-119
inside	121-140	121-139	121-140		120-139
TM (4)	141-163	140-162	141-163		140-162
outside	164-198	163-202	164-203		163-201
TM (5)	199-221	203-25	204-226		202-224
inside	222-240	226-237	227-237		225-236
TM (6)	241-260	238-260	238-260		237-259
outside	261-274	261-269	261-272		260-268
TM (7)	75-292	270-289	273-292		269-291
inside	293-314	290-318	293-323		292-311

TABLE 13

GENBANK IDENTIFIER	MOUSE HOMOLOG	061779	061780	061781	061784	061785
XM_061779			42% (63%)	36% (57%)	43% (64%)	40% (61%)
XM_061780	MOR239-6 (AY073489) 90% (93%)	42% (63%)		41% (60%)	44% (62%)	46% (67%)
XM_061781		36% (57%)	41% (60%)		43% (63%)	40% (61%)

IOCID: <WO 03089583A2_1_>

XM_061784	MOR223 ~>85%	43% (64%)	44% (62%)	43% (63%)		81% (87%)
XM_061785	MOR223 ~>85%	40% (61%)	46% (67%)	40% (61%)	81% (87%)	

TABLE 14

TABLE 15

Clone ID (gene code)	ACCN	Predominant sites of expression	Other expression sites	Cytogenetic locus
TMD1030 (SEQ ID NO 185-186)	XM_166853	spleen	liver	11q12.2
TMD1029 (SEQ ID NO 187-188)	XM_166854	spleen, lymphocytes, liver	brain, heart, lung, lymph node	11q12.2
TMD1028 (SEQ ID NO 189-190)	XM_166855	spleen, lymphocytes	liver	11q12.2
TMD0621 (SEQ ID NO 191-192)	XM_166205	spleen	brain, heart, liver, lung and pancreas	11q12.2

TABLE 16

Clone ID	ACCN	Protein length (aa)	domain description
TMD1030	XM_166853	298	Transmembrane domain: 27 - 49 Transmembrane domain: 98 - 120 Transmembrane domain: 140 - 162 Transmembrane domain: 175 - 197 Transmembrane domain: 207 - 226

			Transmembrane domain: 238 - 260 Transmembrane domain: 275 - 292
TMD1029	XM_16684	309	Transmembrane domain: 26 - 48 Transmembrane domain: 61 - 78 Transmembrane domain: 98 - 120 Transmembrane domain: 140 - 162 Transmembrane domain: 196 - 218 Transmembrane domain: 238 - 260 Transmembrane domain: 275 - 292
TMD1028	XM_166855	173	Transmembrane domain: 18 - 40 Transmembrane domain: 61 - 83 Transmembrane domain: 103 - 125 Transmembrane domain: 137 - 156
TMD0621	XM_166205	109	Transmembrane domain: 9-31 Transmembrane domain: 69 - 91

DOCID: <WO 03089583 A1>

DOCID: <WO_____03089583A2 I >

TABLE 17

Clone ID	ACCN	F-oligo	R-oligo
TMD1030	XM_166853	GGGATTTGGTGTCCAACACGAATTTCA (SEQ ID NO 197)	GAGCCTATAATATATGAGCCAGCTACGAGTTGGA (SEQ ID NO 198)
TMD1029	XM_166854	GTCACTGAATTCTATCTTCTGGGATTTGGTGC (SEQ ID NO 199)	AAACCTGTTTGTACAGAGGCATTTATTGAGCC (SEQ ID NO 200)
TMD1028	XM_166855	GATATCATTTTGGGGCTGCATGATACAATTATTGG (SEQ ID NO 201)	CTCCAACCCAGTGAACATCAAGTTAAATCCCAC (SEQ ID NO 202)
TMD0621	XM_166205	TTAAGCTATTAGTTAGTTCATATGTCATGGGTTTCC (SEQ ID NO 203)	CTCATTAATACGATGGCATAGATACATGTAAGAGAG (SEQ ID NO 204)

5

TABLE 18

Clone ID	ACCN	Promoter Sequence (likelihood score)
TMD1030	XM_166853	ATGTTCCATCTAAATGAAGCCTGAGAAACCCAGCACTACCCACTTGTTAG (0.94) (SEQ ID NO 205) ACATCCATTATATAACAGGGTTAATATACTTGTAAAGAATAGCACCTAGA (0.95) (SEQ ID NO 206)
TMD1029	XM_166854	AAATGTATAAATTCTGCATGAAATTGGGGGTGGGGCTTGTACTACTTTTG (0.98) (SEQ ID NO 207)
TMD1028	XM_166855	ATGTTCCATCTAAATGAAGCCTGAGAAACCCAGCACTACCCACTTGTTAG (0.94) (SEQ ID NO 208) ACATCCATTATATAACAGGGTTAATATACTTGTAAAGAATAGCACCTAGA (0.95) (SEQ ID NO 209)

TMD0621	XM_166205	AAATATATATTTTAAATTGGCCAGGCGCGGTGGCTCACGCCTATAATCCC	(0.99) (SEQ ID NO 210)
		GGCTCACGCCTATAATCCCAGCACTTTGGGAGGCCGAGGCAGGTGGATCA	(0.97) (SEQ ID NO 211)
		TCCCAAATATATATATATACACACACACACACACACACACATATATAT	(1.00) (SEQ ID NO 212)
		CACACACACATATATATACACACACATATATTTATAATCATTTAACAACA	(0.91) (SEQ ID NO 213)

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OCID: <WO 03089583A2 I >

TABLE 19

TABLE 19

(from Principles of Internal Medicine, Volume 1, Page 357, 12th Edition, McGraw-Hill Inc.)

DOCID: <WO 03089583A2 I >

OCID: <WO_____03089583A2_I_>

Table 20

Clone ID	ACCN	Gene Name/Description	Predominant Sites of expression	Other expression sites
TMD0077	XM_166914	Homo sapiens olfactory receptor MOR212-1 (LOC219956), mRNA.	pancreas and testis	brain, heart and kidney
TMD0233	XM_069616	Homo sapiens similar to olfactory receptor (LOC135941) mRNA	pancreas	none
TMD0256	XM_066725	Homo sapiens similar to olfactory receptor (LOC139478) mRNA	pancreas	skin and testis
TMD0258	XM_066873	Homo sapiens similar to beta-2 adrenergic receptor (LOC139760) mRNA	pancreas	colon, stomach and testis
TMD0267	XM_089550	Homo sapiens similar to CG5281 gene product (LOC159371) mRNA	pancreas and testis	adrenal gland, bone marrow, colon, heart, intestine(small), kidney, liver, pituitary, prostate, skin, stomach and thyroid
TMD0271	XM_061815	Homo sapiens similar to odorant receptor S18 gene (LOC120010) mRNA	pancreas and testis	PBL, prostate, thymus and uterus
TMD0290	XM_065813	Homo sapiens similar to unnamed protein product (LOC130644) mRNA	pancreas and testis	none
TMD0530	XM_048304	Homo sapiens hypothetical protein DKFZp564A1164 (DKFZP564A1164) mRNA	pancreas	brain, kidney, lung, lymph node, PBL, mammary gland, pituitary, stomach, testis and thyroid
TMD0574	XM_055514	Homo sapiens KIAA1910 protein (KIAA1910) mRNA	brain and pancreas	pituitary
TMD0608	XM_058332	Homo sapiens similar to putative (H. sapiens) (LOC118670) mRNA	pancreas and testis	stomach
TMD0639	XM_058690	Homo sapiens similar to data source:MGD, source key:MGI:96073, evidence:ISS~hexosaminidase A~putative (LOC204249), mRNA.	pancreas and testis	liver, PBL and prostate
TMD0645	XM_085376	Homo sapiens LOC146225 (LOC146225), mRNA.	pancreas and testis	bone marrow, brain, heart, kidney, liver, lung, lymph node, PBL, muscle, pituitary, prostate, skin, spleen, stomach and thymus
TMD0674	XM_059132	Homo sapiens similar to RIKEN cDNA 4930549C01 gene (LOC127309) mRNA	pancreas and testis	brain, pituitary, prostate and stomach
TMD0675	XM_059134	Homo sapiens similar to putative (H. sapiens) (LOC127348) mRNA	pancreas and testis	prostate and stomach
TMD0677	XM_059140	Homo sapiens similar to dJ39G22.2 (novel protein) (H. sapiens) (LOC127391) mRNA	pancreas and testis	prostate and stomach
TMD0726	XM_059639	Homo sapiens similar to hypothetical protein (H. sapiens) (LOC133309) mRNA	pancreas and testis	adrenal gland, brain, prostate and stomach
TMD0727	XM_059654	Homo sapiens similar to testis-specific transporter TST1 (H. sapiens) (LOC133482) mRNA	pancreas and testis	stomach
TMD0739	XM_059812	Homo sapiens similar to putative (H. sapiens) (LOC135886) mRNA	pancreas and testis	liver, lung, mammary gland, ovary, pituitary, prostate and stomach
TMD0753	XM_059954	Homo sapiens similar to putative (H. sapiens) (LOC138240) mRNA	pancreas and testis	none
TMD1111	NM_014386	Homo sapiens polycystic kidney disease 2-like 2 (PKD2L2) mRNA	pancreas and testis	none
TMD1127	NM_054020	Homo sapiens putative ion channel protein CATSPER2 (CATSPER2), mRNA.	pancreas and testis	none

Table 21

Clone ID	ACCN	Protein seq length (aa)	Domain description
TMD0077	XM_166914	310	7 transmembrane receptor (rhodopsin family)
			Transmembrane domains: 27 - 49
			Transmembrane domains: 61 - 83
			Transmembrane domains: 98 - 120
			Transmembrane domains: 141 - 163
			Transmembrane domains: 202 - 224
			Transmembrane domains: 237 - 259
			Transmembrane domains: 274 - 291
TMD0233	XM_069616	310	7 transmembrane receptor (rhodopsin family)
			Transmembrane domain: 26 - 48
			Transmembrane domain: 60 - 77
			Transmembrane domain: 97 - 119
			Transmembrane domain: 140 - 162
			Transmembrane domain: 196 - 218
			Transmembrane domain: 239 - 261
			Transmembrane domain: 272 - 291
TMD0256	XM_066725	308	7 transmembrane receptor (rhodopsin family)
			Transmembrane domain: 27 - 49
			Transmembrane domain: 61 - 83
			Transmembrane domain: 98 - 120
			Transmembrane domain: 140 - 162
			Transmembrane domain: 196 - 218
			Transmembrane domain: 239 - 258
			Transmembrane domain: 273 - 291
TMD0258	XM_066873	335	7 transmembrane receptor (rhodopsin family)
			Transmembrane domain: 10 - 32
			Transmembrane domain: 39 - 61
			Transmembrane domain: 79 - 101
			Transmembrane domain: 121 - 143
			Transmembrane domain: 163 - 185
			Transmembrane domain: 226 - 248
			Transmembrane domain: 263 - 282
TMD0267	XM_089550	324	Integral membrane protein DUF6: 49-161
			Transmembrane domain: 59 - 78
			Transmembrane domain: 91 - 110
			Transmembrane domain: 115 - 137
			Transmembrane domain: 146 - 168
			Transmembrane domain: 183 - 201
			Transmembrane domain: 214 - 236
			Transmembrane domain: 246 - 265

			Transmembrane domain: 270 - 292
			Transmembrane domain: 297 - 316
TMD0271	XM_061815	291	7 transmembrane receptor (rhodopsin family)
			Transmembrane domain: 29 - 51
			Transmembrane domain: 56 - 78
			Transmembrane domain: 83 - 105
			Transmembrane domain: 120 - 142
			Transmembrane domain: 163 - 185
			Transmembrane domain: 190 - 207
			Transmembrane domain: 220 - 239
			Transmembrane domain: 249 - 271
TMD0290	XM_065813	245	Transmembrane domain: 24 - 46
			Transmembrane domain: 61 - 83
			Transmembrane domain: 96 - 118
			Transmembrane domain: 128 - 150
			Transmembrane domain: 162 - 184
			Transmembrane domain: 221 - 243
TMD0530	XM_048304	708	Immunoglobulin domain: 139-206
			Immunoglobulin domain: 326-377
			Transmembrane domain: 511 - 533
TMD0574	XM_055514	696	Leucine rich repeat C-terminal domain: 212-262
			Leucine rich repeat C-terminal domain: 529-579
			Transmembrane domain: 621 - 643
TMD0608	XM_058332	105	Transmembrane domain: 13 - 35
TMD0639	XM_058690	127	Transmembrane domain: 12 - 34
			Transmembrane domain: 44 - 66
TMD0645	XM_085376	248	Transmembrane domain: 113 - 135
			Transmembrane domain: 150 - 169
			Transmembrane domain: 176 - 198
TMD0674	XM_059132	134	Transmembrane domain: 5 - 22
TMD0675	XM_059134	206	Transmembrane domain: 15 - 37
TMD0677	XM_059140	182	Transmembrane: 49 - 71
TMD0726	XM_059639	96	Transmembrane domain: 13 - 35
			Transmembrane domain: 50 - 72
TMD0727	related to XM_059654	719	Transmembrane domain: 108 - 130

			Transmembrane domain: 145 - 164
			Transmembrane domain: 171 - 193
			Transmembrane domain: 229 - 251
			Transmembrane domain: 264 - 286
			Transmembrane domain: 314 - 336
			Transmembrane domain: 421 - 443
			Transmembrane domain: 453 - 475
			Transmembrane domain: 580 - 602
			Transmembrane domain: 668 - 690
			Organic Anion Transporter Polypeptide (OATP) family, C-terminus: 125-473
			Organic Anion Transporter Polypeptide (OATP) family, N-terminus: 558-717
TMD0739	XM_059812	265	Transmembrane domain: 126 - 148
			Transmembrane domain: 185 - 207
TMD0753	XM_059954	161	Transmembrane domain: 26 - 48
TMD1111	NM_014386	609	Ion transporter domain: 284-490
			Transmembrane domain: 34 - 56
			Transmembrane domain: 274 - 296
			Transmembrane domain: 315 - 337
			Transmembrane domain: 364 - 386
			Transmembrane domain: 407 - 429
			Transmembrane domain: 469 - 491
TMD1127	NM_054020	528	Ion transporter domain: 172-340
			Transmembrane domain: 113 - 132
			Transmembrane domain: 147 - 169
			Transmembrane domain: 176 - 198
			Transmembrane domain: 241 - 263
			Transmembrane domain: 276 - 295
			Transmembrane domain: 315 - 337

Table 22

Clone ID	ACCN	Cytogenetic locus	disease linkage
TMD0077	XM_166914	11q12.2	angioedema, hereditary; spastic paraplegia 17; osteoporosis-pseudoglioma syndrome ; pancreatic tumor
TMD0233	XM_069616	7q35	glaucoma 1, open angle, f ;
TMD0256	XM_066725	Xq26.1	x inactivation, familial skewed, 2; panhypopituitarism; thoracoabdominal syndrome; dandy-walker malformation with mental retardation, basal ganglia disease, and seizures; split-hand/foot malformation 2; mental retardation with optic atrophy, deafness
TMD0258	XM_066873	Xq26.1	x inactivation, familial skewed, 2; panhypopituitarism; thoracoabdominal syndrome; dandy-walker malformation with mental retardation, basal ganglia disease, and seizures; split-hand/foot malformation 2; mental retardation with optic atrophy, deafness
TMD0267	XM_089550	10q24.1	corneal dystrophy of bowman layer, type ii; alzheimer disease 6
TMD0271	XM_061815	11p15.4	charcot-marie-tooth disease, type 4b, form 2; deafness, neurosensory, autosomal recessive 18 ;
TMD0290	XM_065813	2p23.1	none
TMD0530	XM_048304	19q13.13	hypocalciuric hypercalcemia, familial, type iii; deafness, autosomal dominant nonsyndromic sensorineural 4; microcephaly, primary autosomal recessive, 2
TMD0574	XM_055514	13q31.1	microcoria, congenital; schizophrenia 7 ;
TMD0608	XM_058332	10q26.3	endometrial carcinoma
TMD0639	XM_058690	15q22.32	cataract, central saccular, with sutural opacities; obesity syndrome
TMD0645	XM_085376	16q23.1	dehydrated hereditary stomatocytosis; pancreatic acinar cancer
TMD0674	XM_059132	1p36.11	breast cancer, ductal, 2; prostate cancer/brain cancer susceptibility; melanoma, cutaneous malignant; inflammatory bowel disease 7 ;
TMD0675	XM_059134	1p33	carcinoma of pancreas
TMD0677	XM_059140	1p34.2	deafness, autosomal dominant nonsyndromic sensorineural 2; porphyria cutanea tarda; hypercholesterolemia, familial, ptosis, hereditary congenital 1 ;
TMD0726	XM_059639	10q11.22	none
TMD0727	related to XM_059654	5q21.1	anemia, dyserythropoietic congenital, type iii; dyslexia, specific, 1; colorectal cancer, hereditary nonpolyposis, type 7; cataract, central saccular, with sutural opacities
TMD0739	XM_059812	7q11.23	autism, susceptibility to, 1; muscular dystrophy, limb-girdle, type 1d; aneurysm, intracranial
TMD0753	XM_059954	9q21.12	hemophagocytic lymphohistiocytosis, familial, 1; amyotrophic lateral sclerosis with frontotemporal dementia
TMD1111	NM_014386	5q31	none
TMD1127	NM_054020	15q13-q15	nanophthalmos 2; spastic paraplegia 11, autosomal recessive; corpus callosum, agenesis of, with neuronopathy; pancreatic acinar carcinoma

TABLE 23

CODE	ACCN	PRIMERS	PROMOTER
TMD0077 (SEQ ID NO 214-215)	XM_166914	TCATGGATCACCAGCTCCACGCTC (Forward) (SEQ ID NO 256) CACCAAGATCACCACCATGGAAGCA (Reverse) (SEQ ID NO 257)	GGATTCAGGCCTTTTAAACCCCACTCAGTGGGTGCATGGCAGGGCTTTGA (0.88) (SEQ ID NO 258)
TMD0233 (SEQ ID NO 216-217)	XM_069616	TGCTGACGAATCTTATGAACCAGG (Forward) (SEQ ID NO259) TCACGTCAGCCTCTCCTTCCTCAGTG (Reverse) (SEQ ID NO 260)	TCACAAATCATATAAATTAGGGGAAAGAGAGAGGCAGGTATACTCTAAAA (0.96) (SEQ ID NO 261) AATTTCTTATTTAAAAGACCTCAGAAATGTCACCATGCTTAGTTATTTTA (0.95) (SEQ ID NO 262)
TMD0256 (SEQ ID NO 218-219)	XM_066725	GGCCATGGACAATGTCACAGCAG (Forward) (SEQ ID NO 263) AGCAGACACATACTGGGCCATTCATAACCAC (Reverse) (SEQ ID NO 264)	GGTACTATTCTATATTTTGGGCACACAGCAATGAAGAAAACAGAAAAACC (0.93) (SEQ ID NO 265) CTGGGTTTCATAAATATGGAGCAGAAAGTTTTTACAAATATAGAACAGCA (0.92) (SEQ ID NO 266) TAGAATGTGTTATAAAAAATGAAGCAGGGCTAGGGGAAAGAGATGGGTGA (0.91) (SEQ ID NO 267)
TMD0258 (SEQ ID NO 220-221)	XM_066873	CCTCATTGGCTTCCTCCCACTCG (Forward) (SEQ ID NO 268) GCCATCAAACTCTGAGCTGGAGATAGTGAC (Reverse) (SEQ ID NO 269)	CCAAGGAACTTTTAAAACTCCCATTGCACAGTTACCACCCAGAATAATTA (0.97) (SEQ ID NO 270 CATCCTGGAATATATTTGCGTCCAACTCTGCACCTTGCTCTCTATTCCCT (0.96) (SEQ ID NO 271 CTGGGGCCCCTCAAAAAGCTCACCTTCCCTCACTTCCCACTTCAACTGAT (0.91) (SEQ ID NO 272)
TMD0267 (SEQ ID NO 222-223)	XM_089550	TGGCCTCGTTGAAAGTGTCATCATCC (Forward) (SEQ ID NO 273 TTGGTACCATTTACGAATGGCCGC (Reverse) (SEQ ID NO 274)	AAACGGCATTTTAAAAATGCAGGTTTAAATTGTTATCCTCATCTATGGTT (0.98) (SEQ ID NO 275)
TMD0271 (SEQ ID NO 224-225)	XM_061815	CTGGACTTGAGCAGTACCACGTCTGGATC (Forward) (SEQ ID NO 276) CATATTCCCACAGCAATTTTGACAATGG (Reverse) (SEQ ID NO 277)	ATTTTGGTTATATATAGAGGAGTCTAGGAAAAGACTCGTGGGTCTGATTC (0.97) (SEQ ID NO 278) TACTCATATTTATATAGCAGCAACTTACATTGACCCAGGGAGAACTCAGT (0.94) (SEQ ID NO 279)
TMD0290 (SEQ ID NO 226-227)	XM_065813	GTTACCCACCCAACCGTCACGACC (Forward) (SEQ ID NO 280) CAGGCGATGCCAGAGAAGACGATG (Reverse) (SEQ ID NO 281)	CTAGAATTTACATAAAAAGGACTGGAGGAGCTTTTGCAGCAACTTTGCAT (0.97) (SEQ ID NO 282) TTTTCTTCTTTTAAAAACACGCTTTCACTCTCAAAACAGCAGAGAATGAA (0.98) (SEQ ID NO 283) AACTGGGGTCTATAAGAGAGCCAGGGCACTTATTCATCCAAGGGCAGATG (0.99) (SEQ ID NO 284)
TMD0530 (SEQ ID NO 228-229)	XM_048304	CTATGACTTCAACCCACACCTGGGCA (Forward) (SEQ ID NO 285) AAGGTCGCCAACTTGTCCTGGCTC (Reverse) (SEQ ID NO 286)	GGGCGGGAGTAAAAGGCAGAGTCCAATTCCACCGGCCCCCAGTGTGGGTG (0.86) (SEQ ID NO 287)

CODE	ACCN	PRIMERS	PROMOTER
TMD0574 (SEQ ID NO 230-231)	XM_055514	TCAATGCCATGCCCAAACTGAGGA (Forward) (SEQ ID NO 288) CAACACCGAGATGGACACCCTGCT (Reverse) (SEQ ID NO 289)	CTTTTAAGGTTAAAAATGTGGGTTTTAGATGATTGTCCTTTCTAAACAGC (0.99) (SEQ ID NO 290) TCAGGATGTCTAAAAAAGATCTCTCTAGTGTACACACGTGCACACACACA (0.97) (SEQ ID NO 291) AGTAACTCTATTTAAAAGACCTAAAAATTTCAAATCCTAAAATGATCTAT (0.90) (SEQ ID NO 292) AATAAATGTTTTAAAAGCACTCCTTTCCGAATGGTGGAGCTGGTGGGGGC (0.91) (SEQ ID NO 293)
TMD0608 (SEQ ID NO 232-233)	XM_058332	CTCAGGACGAAGATCATGATCGGCATC (Forward) (SEQ ID NO 294) GAAGATTTTTGTGCCCAGCTTTCCCAAG (Reverse) (SEQ ID NO 295)	TATTCTCACTTATAAGTGGGAGCTAAGCCATGAGGGCACCAAGGCATAAG (0.99) (SEQ ID NO 296) TTACATATGTATACATGTGCCATGCTGGTGTGCTGCACCCATTAACTCGT (0.96) (SEQ ID NO 297)
TMD0639 (SEQ ID NO 234-235)	XM_058690	TCCATGCTCAGCTTCATCTCAGCTACC (Forward) (SEQ ID NO 298) TCCATCTCAGACCTTGGCCCTTCA (Reverse) (SEQ ID NO 299)	AAATAACCCCATTAAAAAGTGGGCAAAGGGCATGAACACTTTTCAAAAGA (1.00) (SEQ ID NO 300)
TMD0645 (SEQ ID NO 236-237)	XM_085376	AGGACGGTAAGGAGCCATCGGACA (Forward) (SEQ ID NO 301) CTTGCCAGGTTCTGGTGGCTTGG (Reverse) (SEQ ID NO 302)	TCTTTTTGTCTATAAATAGGACTTTGATTTTCTGGACTAGAGAATTGTAT (0.94) (SEQ ID NO 303)
TMD0674 (SEQ ID NO 238-239)	XM_059132	ACGACTCCAAGAACAGCAAGGCCG (Forward) (SEQ ID NO 304) AAGGTAACATCGGCAGAGGCCAGC (Reverse) (SEQ ID NO 305)	GCTAGCATTTTTTAAAAGCTGATGTCTTCACTGGGCACGGGGACTCACAC (0.94) (SEQ ID NO 306)
TMD0675 (SEQ ID NO 240-241)	XM_059134	CGGCCAGGTACCAAAGCTCAGCTG (Forward) (SEQ ID NO 307) GCCAGATTCAGGAGGGAATGGAAGAGAAC (Reverse) (SEQ ID NO 308)	TGATCTACTTTTTAAAAGGATCATGCTGGCTGCTGGTGGGATTTAGGATA (0.91) (SEQ ID NO 309) TGATAGTGATAAAAAAAAAGTGGCCAGATTTTGGTTATATTTTGAAATAAA (0.99) (SEQ ID NO 310) TATAGTGATATTTAAAGCCAGGGGTCTGGGTGAGATAACTGATGGAATGA (0.93) (SEQ ID NO 311) ATTGGAGGACTATAAAGAGGGGAGTCATTAAAATGGTGCTAAGAAGCTGA (0.96) (SEQ ID NO 312) AGAGGGGAGTCATTAAAATGGTGCTAAGAAGCTGAGCTACAAGCAGTGGT (0.97) (SEQ ID NO 313) GACATTCCACCCAAAAAATGCCACTGGATGAAGTCCCCTCCTTCCATTAA (0.92) (SEQ ID NO 314)

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CODE	ACCN	PRIMERS	PROMOTER
TMD0677 (SEQ ID NO 242-243)	XM_059140	TTGGGAGAGACTAGTGCACCTCAGCA (Forward) (SEQ ID NO 315) GAGCAATCCCTCTTCGTGGCAGGT (Reverse) (SEQ ID NO 316)	AAAAGTGCTTTTAAACAGGGGGGGTGGAGGGGCTTATGAGAAGGGGACCA (1.00) (SEQ ID NO 317) CCATTTCTACTAAAAATGCAGAGATCAGCCAGGCGTGGCACGTGCCTGTA (0.95) (SEQ ID NO 318) AAAAAAAAAAAAAAAAAAGCCCTGTTTATATCCTACCTCCTTGCTGGGTGC (0.98) (SEQ ID NO 319) AAAATAAAAATAAAAAAATCCCATCTCCTCACATTTCCATTCAACCTCAAT (0.93) (SEQ ID NO 320)
TMD0726 (SEQ ID NO 244-245)	XM_059639	ACTTCCAAACATCTACAACTCCTCAGAGTCTCATT (Forward) (SEQ ID NO 321) TGCAGCACCATCATGTAAGGGACAA (Reverse) (SEQ ID NO 322)	TTTTTTAAACTATAAAAAGTGGGGATCAGAAAACACAGTCATAAGGGAAA (0.97) (SEQ ID NO 323) GTATATGCTATATATATCAGGATTCACTTTAATGGCATTGAGTTCCAGGA (0.98) (SEQ ID NO 324) ATAAACAATTTAAAAATTAGCCCACCATGGTGGTACACACCTGTCGTTCT (0.99) (SEQ ID NO 325) AAAAAGTGAAAAAAAAAGGTGAGGGAGACTTTAACTTTCTGAAATATATT (0.92) (SEQ ID NO 326)
TMD0727 (SEQ ID NO 246-247)	XM_059654 (related to)	CCAAGAAGCCGGGAGAAGTGGATG (Forward) (SEQ ID NO 327) TGACAGAGCTAGGCATATGAGCACTGGA (Reverse) (SEQ ID NO 328)	CTAAAGAGCTTATATATCAGCCTAAGAAAAGAAAACCAATAAGAAGTTGC (0.96) (SEQ ID NO 329)
TMD0739 (SEQ ID NO 248-249)	XM_059812	GCAGTTGGTTCAGAACCGAGATCACC (Forward) (SEQ ID NO 330) GGCAGATGGGGATACATTTATTCTCTGGG (Reverse) (SEQ ID NO 331)	ACTAAAAATACAAAAAAGTAGCCGGGTATGGTGGTAGGCGCCTATAATCC (0.93) (SEQ ID NO 332) GGTAGGCGCCTATAATCCCAGCTACTTGGGAGGCTGAGGCAGGAGAATTG (0.92) (SEQ ID NO 333)
TMD0753 (SEQ ID NO 250-251)	XM_059954	TCGGCTTGGAAATCAGAATGAGAAGG (Forward) (SEQ ID NO 334) TGCACAAAGAATGATTGCAGCAGTGAGTAG (Reverse) (SEQ ID NO 335)	AAAAGGCTTATATAAAAGGGTTTTGTTTTGTTTTGTTTTGAGACGGAGTT (0.97) (SEQ ID NO 336) GGCCAACTTATATAAAAGGTTTATGTTTTTGTTCTGATAATTTCGTTTCT (0.91) (SEQ ID NO 337) AAGTTAAGTTTTAAAAAGAACAGGCTACAAAGTTATAGCTATGGGGTGAT (0.96) (SEQ ID NO 338)
TMD1111 (SEQ ID NO 252-253)	NM_014386	GGGCGGTGTAGTGCAGGTCCG (Forward) (SEQ ID NO 339) CCTCCAGTTGCAGGGAATTCTGCC (Reverse) (SEQ ID NO 340)	AATTCAAATATTTAAAACGGACTGTCTCCTCTTCACAAAAGTCTAGATCT (0.92) (SEQ ID NO 341)
TMD1127 (SEQ ID NO 254-255)	NM_054020	GGCTGTTGAGCAGGCTTCATGTGC (Forward) (SEQ ID NO 342) CTCCTCTGGATGATCTGCCGCTTG (Reverse) (SEQ ID NO 343)	ATTGGGTGCATATATATTTAGGATAGTTAGCTCTTCTTGTTGAATTGATC (0.89) (SEQ ID NO 344)

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XCID: <WO_____03089583A2 1 >

DOCID: <WO 03089583A2_I_>

CLAIMS:

1. A method of detecting an immune system cell, comprising:

contacting a sample comprising cells with a polynucleotide specific for TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), or TMD0890 (XM_060959) of claim 28, under conditions effective for said polynucleotide to hybridize specifically to said gene, and

detecting specific hybridization.

2. A method of claim 1, wherein said detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization.

3. A method of detecting an immune system cell, comprising:

contacting a sample comprising cells with a binding partner specific for a polypeptide coded for by TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), or TMD0890 (XM_060959) of claim 28, under conditions effective for said binding partner bind specifically to said polypeptide, and

detecting specific binding.

4. A method of claim 3, wherein said detecting is performed by:

immunocytochemistry, immunoprecipitation, or Western blot.

5. A method of delivering an agent to an immune cell, comprising:

contacting an immune cell with an agent coupled to binding partner specific for a polypeptide coded for by TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), or TMD0890 (XM_060959) of claim 28 , whereby said agent is delivered to said cell.

6. A method of claim 5, wherein the agent is a therapeutic agent or an imaging agent.

7. A method of claim 5, wherein the agent is cytotoxic.

8. A method of claim 5, wherein the binding partner is an antibody.

9. A method of modulating the maturation of an immune system cell, comprising:

contacting said cell with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959) of claim 28, whereby the maturation of an immune cell is modulated.

10. A method of modulating interactions between lymphoid and non-lymphoid immune system cells, comprising:

contacting said cells with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959) of claim 28, whereby the interaction is modulated.

11. A method of expressing a heterologous polynucleotide in immune system cells, comprising:

expressing a nucleic acid construct in immune system cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected from SEQ ID NOS 5, 10, 11, 16-19, 29-32, 37-39, 44-46, 51-54, and 59-62.

12. A method of treating an immune system disease, comprising:

administering to a subject in need thereof a therapeutic agent which is effective for regulating expression of a gene, or polypeptide encoded thereby, selected from TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025

(XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959) of claim 28.

13. A method of claim 12, wherein said agent is an antibody or an antisense which is effective to inhibit translation of said gene.

14. A method of diagnosing an immune disease associated with abnormal gene expression, or determining a subject's susceptibility to such disease, comprising:

assessing the expression of a gene, or polypeptide encoded thereby, selected from TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959) of claim 28 in a tissue sample comprising immune system cells.

15. A method of claim 14, wherein assessing is:

measuring expression levels of said gene, determining the genomic structure of said gene, determining the mRNA structure of transcripts from said gene, or measuring the expression levels of polypeptide coded for by said gene.

16. A method of claim 14, wherein said assessing detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization, and

using a polynucleotide probe having a sequence selected from TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959) of claim 28, or a polynucleotide probe having 95% sequence identity or more to a sequence set forth in SEQ ID NOS 1, 6, 12, 20, 25, 33, 40, 47, or 55, effective specific fragments thereof, or complements thereto.

17. A method of assessing a therapeutic or preventative intervention in a subject having an

immune system disease, comprising,

determining the expression levels of a gene, or polypeptide encoded thereby, selected from TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959) of claim 28 in a tissue sample comprising immune system cells.

18. A method of claim 17, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

19. A method for identifying an agent that modulates the expression of a gene or polypeptide in the immune system gene complex, comprising,

contacting an immune system cell with a test agent under conditions effective for said test agent to modulate the expression of a gene selected from TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959) of claim 28, or the biological activity of a polypeptide encoded thereby, in said immune system cell, and

determining whether said test agent modulates said gene or polypeptide.

20. A method of claim 19, wherein said agent is an antisense polynucleotide which is effective to inhibit translation of said gene or an antibody specific for said polypeptide.

21. A method of detecting polymorphisms in a gene in the immune system gene complex, comprising: comparing the structure of:

genomic DNA or RNA or cDNA or a polypeptide comprising all or part of a gene selected from TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959) of claim 28 with the structure of SEQ ID NOS 1, 6, 12, 20, 25, 33, 40, 47, or 55.

22. A method of claim 20, wherein said polymorphism is a nucleotide deletion, substitution, inversion, or transposition.

23. A method of identifying a genetic basis for an immune disease or disease-susceptibility, comprising:

determining the association of an immune disease or disease-susceptibility with a nucleotide sequence present in a genome comprising the gene complex of claim 28.

24. A method of claim 23, wherein determining is performed by producing a human-linkage map of said complex.

25. A method of claim 23, wherein determining is performed by comparing the nucleotide sequences between normal subjects and subjects having an immune system disease.

26. A non-human, transgenic mammal, or a cell thereof, whose genome comprises a functional disruption of a gene selected from TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959) of claim 28, or a mouse homolog thereof, and which has a defect in immune system function.

27. A method of selecting a gene predominantly expressed in immune system cells from a database comprising polynucleotide sequences for genes, comprising:

displaying, in a computer-readable medium, a polynucleotide sequence or polypeptide sequence for a gene selected from TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959), or complements to the polynucleotides sequence,

wherein said displayed sequences have been retrieved from said database upon selection by a user.

28. A composition consisting essentially of the 1q22 immune gene complex, comprising TMD0024 (XM_060945), TMD1779 (XM_060946), TMD0884 (XM_060947), TMD0025 (XM_060948), TMD1780 (XM_089422), TMD1781 (XM_089421), TMD0304 (XM_060956), TMD0888 (XM_060957), and TMD0890 (XM_060959) genes, or a fragment thereof comprising at least two said genes.

29. A composition of claim 28, wherein said complex consists essentially of the chromosome region between STS markers SHGC-81033 and SHGC-145403, or a fragment thereof comprising at least two said genes.

30. A composition of claim 28, wherein said complex consists essentially of the chromosome region between STS markers SHGC-81033 and D1S3249, G15944, GDB:191077, or GDB:196442, or a fragment thereof comprising at least two said genes.

31. A composition of claim 28, wherein said complex consists essentially of the chromosome region between STS markers RH118729 and D1S2577 or SHGC-145403, or a fragment thereof comprising at least two said genes.

32. A method of detecting an immune system cell, comprising:

contacting a sample comprising cells with a polynucleotide specific for a XM_062147 (SEQ ID NO 63) or XM_061676 (SEQ ID NO 69) of claim 59 under conditions effective for said polynucleotide to hybridize specifically to said gene, and

detecting specific hybridization.

33. A method of claim 32, wherein said detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization.

34. A method of detecting an immune system cell, comprising:

contacting a sample comprising cells with a binding partner specific for a polypeptide coded for XM_062147 (SEQ ID NO 64) or XM_061676 (SEQ ID NO 70) of claim 59 under conditions effective for said binding partner bind specifically to said polypeptide, and

detecting specific binding.

35. A method of claim 34, wherein said detecting is performed by:

immunocytochemistry, immunoprecipitation, or Western blot.

36. A method of delivering an agent to an immune cell, comprising:

contacting an immune cell with an agent coupled to binding partner specific for XM_062147 (SEQ ID NO 64) or XM_061676 (SEQ ID NO 70) of claim 59, whereby said agent is delivered to said cell.

37. A method of claim 36, wherein the agent is a therapeutic agent or an imaging agent.

38. A method of claim 36, wherein the agent is cytotoxic.

39. A method of claim 36, wherein the binding partner is an antibody.

40. A method of modulating the maturation of an ~~immune~~ system cell, ~~comprising~~:

contacting said cell with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from XM_062147 (SEQ ID NO 63 or 64) or XM_061676 (SEQ ID NO 69 or 70) of claim 59, whereby the maturation of an immune cell is modulated.

41. A method of modulating interactions between lymphoid and non-lymphoid immune system cells, comprising:

contacting said cells with an agent effective to modulate a gene, or polypeptide encoded thereby, selected from XM_062147 (SEQ ID NO 63 or 64) or XM_061676 (SEQ ID NO 69 or 70) of claim 59, whereby the interaction is modulated.

42. A method of expressing a heterologous polynucleotide in immune system cells, comprising:

expressing a nucleic acid construct in immune system cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is SEQ ID NOS 65, 66, 72, 73, 74, or 75.

43. A method of treating an immune system disease, comprising:

administering to a subject in need thereof a therapeutic agent which is effective for regulating expression of a gene, or polypeptide encoded thereby, selected from XM_062147 (SEQ ID NO 63 or 64) or XM_061676 (SEQ ID NO 69 or 70) of claim 59.

44. A method of claim 43, wherein said agent is an antibody or an antisense which is effective to inhibit translation of said gene.

45. A method of diagnosing an immune disease associated with abnormal gene expression, or determining a subject's susceptibility to such disease, comprising:

assessing the expression of a gene, or polypeptide encoded thereby, selected from XM_062147 (SEQ ID NO 63 or 64) or XM_061676 (SEQ ID NO 69 or 70) of claim 59 in a tissue sample comprising immune system cells.

46. A method of claim 45, wherein assessing is:

measuring expression levels of said gene, determining the genomic structure of said gene, determining the mRNA structure of transcripts from said gene, or measuring the expression levels of polypeptide coded for by said gene.

47. A method of claim 45, wherein said assessing detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR,

RACE PCR, or *in situ* hybridization, and

using a polynucleotide probe having a sequence selected from SEQ ID NOS 67, 68, 76, and 77.

48. A method of assessing a therapeutic or preventative intervention in a subject having an immune system disease, comprising,

determining the expression levels of a gene, or polypeptide encoded thereby, selected from XM_062147 (SEQ ID NO 63 or 64) or XM_061676 (SEQ ID NO 69 or 70) of claim 59 in a tissue sample comprising immune system cells.

49. A method of claim 48, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

50. A method for identifying an agent that modulates the expression of a gene or polypeptide in the immune system gene complex, comprising,

contacting an immune system cell with a test agent under conditions effective for said test agent to modulate the expression of XM_062147 (SEQ ID NO 63 or 64) or XM_061676 (SEQ ID NO 69 or 70) of claim 59, or a polypeptide encoded thereby, in said immune system cell, and

determining whether said test agent modulates said gene.

51. A method of claim 50, wherein said agent is an antisense polynucleotide to a target polynucleotide sequence selected from SEQ ID NOS 63 or 69 and which is effective to inhibit translation of said gene.

52. A method of detecting polymorphisms in a gene in the immune system gene complex, comprising:

comparing the structure of: genomic DNA or RNA or cDNA comprising all or part of an allele of XM_062147 or XM_061676 with SEQ ID NOS 63 or 69 of claim 59.

53. A method of claim 52, wherein said polymorphism is a nucleotide deletion, substitution,

inversion, or transposition.

54. A non-human, transgenic mammal whose genome comprises a functional disruption of a gene represented by XM_062147 (SEQ ID NO 63) or XM_061676 (SEQ ID NO 69) of claim 59, and which has a defect in immune system function.

55. A mammalian immune system cell whose genome comprises a functional disruption of a gene represented by XM_062147 (SEQ ID NO 63) or XM_061676 (SEQ ID NO 69) of claim 59, and which has a defect in immune system function.

56. A mammalian cell of claim 55, wherein said cell is a mouse cell.

57. A non-human, transgenic mammal, or a cell thereof, comprising a gene operatively linked to an expression control sequence effective to express said gene in immune system, wherein said sequence is SEQ ID NOS 65, 66, 71, 72, 73, 74, or 75.

58. A method of selecting a gene predominantly expressed in immune system cells from a database comprising polynucleotide sequences for genes, comprising:

displaying, in a computer-readable medium, a polynucleotide sequence or polypeptide sequence for XM_062147 (SEQ ID NO 63 or 64) or XM_061676 (SEQ ID NO 69 or 70) of claim 59, or complements to the polynucleotides sequence,

wherein said displayed sequences have been retrieved from said database upon selection by a user.

59. A composition comprising:

bone marrow specific genes consisting essentially of XM_062147 (SEQ ID NO 63 or 64) and XM_061676 (SEQ ID NO 69 or 70), or polypeptides thereof.

60. A method of detecting a kidney cell, comprising:

contacting a sample comprising cells with a polynucleotide specific for a polynucleotide, or a naturally-occurring polymorphisms thereof, of claim 81 under conditions effective for said polynucleotide to hybridize specifically to said gene, and

detecting specific hybridization.

61. A method of claim 60, wherein said detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization.

62. A method of detecting an kidney cell, comprising:

contacting a sample comprising cells with a binding partner specific for a polypeptide coded for by a polynucleotide of claim 81, or a naturally-occurring polymorphism thereof, under conditions effective for said binding partner bind specifically to said polypeptide, and

detecting specific binding.

63. A method of claim 62, wherein said detecting is performed by: immunocytochemistry, immunoprecipitation, or Western blot.

64. A method of delivering an agent to a kidney cell, comprising:

contacting a kidney cell with an agent coupled to binding partner specific for polypeptide coded for by a polynucleotide of claim 81, or a naturally-occurring polymorphism thereof, whereby said agent is delivered to said cell.

65. A method of claim 64, wherein the agent is a therapeutic agent, a cytotoxic agent, or an imaging agent.

66. A method of claim 64, wherein the binding partner is an antibody.

67. A method of modulating a kidney cell, comprising:

contacting said cell with an agent effective to modulate a polynucleotide, or polypeptide encoded thereby, or a naturally-occurring polymorphism thereof, of claim 81, whereby the kidney cell is modulated.

68. A method of assessing kidney function, comprising:

detecting a polypeptide coded for by a polynucleotide of claim 81, or a naturally-occurring polymorphism thereof, or fragments thereof, in a body fluid, whereby the amount of said polypeptide in said fluid is a measure of kidney function.

69. A method of claim 68, wherein said detecting is performed using an antibody which is specific for said polypeptide.

70. A method of claim 69, wherein said detecting is performed by RIA, ELISA, or Western blot.

71. A method of expressing a heterologous polynucleotide in kidney cells, comprising:

expressing a nucleic acid construct in kidney cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected from SEQ ID NOS. 106, 109, 110, 113, 114, 117, 118, 121, 124, 125, 128-130, 133, 134, 137, 140, 141, 144, 147, 148, and 151.

72. A method of diagnosing a kidney disease associated with abnormal gene expression, or determining a subject's susceptibility to such disease, comprising:

assessing the expression of a polynucleotide of claim 81, or a polypeptide encoded thereby, or naturally-occurring polymorphisms thereof, in a tissue sample comprising kidney cells.

73. A method of claim 72, wherein assessing is:

measuring expression levels of said gene, determining the genomic structure of said gene, determining the mRNA structure of transcripts from said gene, or measuring the expression levels of polypeptide coded for by said gene.

74. A method of assessing a therapeutic or preventative intervention in a subject having a kidney disease, comprising,

determining the expression levels of a polynucleotide of claim 81, a naturally-occurring polymorphism thereof, or polypeptide encoded thereby, in a tissue sample

comprising kidney cells.

75. A method of claim 74, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

76. A method for identifying an agent that modulates the expression of a polynucleotide or polypeptide selectively expressed in kidney cells, comprising,

contacting an kidney cell with a test agent under conditions effective for said test agent to modulate the expression of a polynucleotide of claim 81, or a naturally-occurring polymorphism thereof, or the biological activity of a polypeptide encoded thereby, in said kidney cell, and

determining whether said test agent modulates said gene or polypeptide.

77. A non-human, transgenic mammal whose genome comprises a functional disruption of a gene represented by a polynucleotide of claim 81, or a homolog thereof, and which has a defect in kidney function.

78. A mammalian kidney cell whose genome comprises a functional disruption of a gene represented by a polynucleotide of claim 81, or a homolog thereof, and which has a defect in kidney function.

79. A mammalian cell of claim 78, wherein said cell is a mouse cell.

80. A method of selecting a gene predominantly expressed in kidney cells from a database comprising polynucleotide sequences for genes, comprising:

displaying, in a computer-readable medium, a polynucleotide sequence, or a polypeptide encoded thereby, of claim 81, or complements to the polynucleotides sequence,

wherein said displayed sequences have been retrieved from said database upon selection by a user.

81. A composition comprising two or more of the following polynucleotides expressed selectively in kidney:

TMD0049 (XM_057351), TMD0190 (XM_087157), TMD0242 (XM_088369), TMD0335 (XM_089960), TMD0371, TMD0374, TMD0469 (XM_038736), TMD0719 (XM_059548), TMD0731 (XM_059703), TMD0785 (XM_060310), TMD0841 (XM_060623), TMD1114 (NM_019841), and/or TMD 1148 (XM_087108).

82. A method of detecting a pancreas cell, comprising:

contacting a sample comprising cells with a polynucleotide specific for TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785, of claim 113 under conditions effective for said polynucleotide to hybridize specifically to said gene, and

detecting specific hybridization.

83. A method of claim 82, wherein said detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization.

84. A method of detecting a pancreas cell, comprising:

contacting a sample comprising cells with a binding partner specific for a polypeptide coded for by TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785, of claim 113 under conditions effective for said binding partner bind specifically to said polypeptide, and, detecting specific binding.

85. A method of claim 84, wherein said detecting is performed by:

immunocytochemistry, immunoprecipitation, or Western blot.

86. A method of delivering an agent to a pancreas cell, comprising:

contacting a pancreas cell with an agent coupled to binding partner specific for

TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785, of claim 113, whereby said agent is delivered to said cell.

87. A method of claim 86, wherein the agent is a therapeutic agent or an imaging agent.

88. A method of claim 86, wherein the agent is cytotoxic.

89. A method of claim 86, wherein the binding partner is an antibody.

90. A method of modulating a pancreas cell, comprising:

contacting said cell with an agent effective to modulate TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785, or the biological activity of a polypeptide encoded thereby, of claim 113, whereby the pancreas cell is modulated.

91. A method of assessing pancreas function, comprising:

detecting a polypeptide coded for TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785, or fragments thereof, in a body fluid, whereby the amount of said polypeptide in said fluid is a measure of pancreas function.

92. A method of claim 91, wherein said detecting is performed using an antibody which is specific for said polypeptide.

93. A method of claim 91, wherein said detecting is performed by RIA, ELISA, or Western blot.

94. A method of expressing a heterologous polynucleotide in pancreas cells, comprising:

expressing a nucleic acid construct in pancreas cells, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is SEQ ID NOS 156-161, 166, 179, or 180.

95. A method of diagnosing a pancreas disease associated with abnormal gene expression,

or determining a subject's susceptibility to such disease, comprising:

assessing the expression of TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785, or polypeptide encoded thereby, of claim 113 in a tissue sample comprising pancreas cells.

96. A method of claim 95, wherein assessing is:

measuring expression levels of said gene, determining the genomic structure of said gene, determining the mRNA structure of transcripts from said gene, or measuring the expression levels of polypeptide coded for by said gene.

97. A method of claim 95, wherein said assessing is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization, and

using a polynucleotide probe having a sequence selected from SEQ ID NOS 154, 155, 164, 165, 169, 170, 173, 174, 177, 178, or a complement thereto.

98. A method of assessing a therapeutic or preventative intervention in a subject having a pancreas disease, comprising,

determining the expression levels of TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785, or a polypeptide encoded thereby, of claim 113 in a tissue sample comprising pancreas cells.

99. A method of claim 98, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

100. A method for identifying an agent that modulates the expression of TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785, or the biological activity of a polypeptide encoded thereby, comprising,

contacting a pancreas cell with a test agent under conditions effective for said test agent to modulate the expression of TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785 of claim 113, or the biological activity of a polypeptide encoded thereby, in said

pancreas cell, and

determining whether said test agent modulates said gene or polypeptide.

101. A method of claim 100, wherein said agent is an antisense polynucleotide to a target polynucleotide sequence selected from SEQ ID NO 152, 162, 167, 171, or 175 and which is effective to inhibit translation of said gene.

102. A method of detecting polymorphisms in TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785, comprising,

comparing the structure of: genomic DNA or RNA or cDNA comprising all or part of an allele of TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785,

with SEQ ID NOS 152, 153, 162, 163, 167, 168, 171, 172, 175, or 176 of claim 113.

103. A method of claim 102, wherein said polymorphism is a nucleotide deletion, substitution, inversion, or transposition.

104. A method of identifying a pancreatic disease or pancreatic disease-susceptibility, comprising:

determining the association of a pancreatic disease or pancreatic disease-susceptibility with a nucleotide sequence present within the pancreatic gene complex of claim 113.

105. A method of claim 104, wherein the pancreatic gene complex is from LOC160025-LOC119954.

106. A method of claim 104, wherein determining is performed by producing a human-linkage map of said complex.

107. A method of claim 104, wherein determining is performed by comparing the nucleotide sequences between normal subjects and subjects having a pancreas disorder.

108. A non-human, transgenic mammal whose genome comprises a functional disruption of a gene represented by TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785

of claim 113, and which has a defect in pancreas function.

109. A mammalian pancreas cell whose genome comprises a functional disruption of a gene represented by TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785 of claim 113, and which has a defect in pancreas function.

110. A mammalian cell of claim 109, wherein said cell is a mouse cell.

111. A pancreas cell, comprising a gene operatively linked to an expression control sequence effective to express said gene in pancreas, wherein said sequence is SEQ ID NOS 156-161, 179, or 180.

112. A method of selecting a gene predominantly expressed in pancreas cells from a database comprising polynucleotide sequences for genes, comprising:

displaying, in a computer-readable medium, a polynucleotide sequence or polypeptide sequence for TMD0986, XM_061780, XM_061781, XM_061784, or XM_061785 of claim 113, or complements to the polynucleotides sequence,

wherein said displayed sequences have been retrieved from said database upon selection by a user.

113. A composition comprising: a pancreas specific gene consisting essentially of TMD0986, XM_061780, XM_061781, XM_061784, and/or XM_061785, or a polypeptide encoded thereby.

114. An isolated polynucleotide comprising a polynucleotide sequence which codes without interruption for a human TMD0986 having an amino acid sequence set forth in SEQ ID NO 153 , or a complement thereto.

115. An isolated polynucleotide comprising,

a human TMD0986 polynucleotide sequence having 90% or more nucleotide sequence identity to the polynucleotide sequence set forth in SEQ ID NO 152 along its entire

length, which codes without interruption for human TMD0986, or a complement thereto, and which has G-protein coupling activity.

116. An isolated humansTMD0986 polypeptide comprising the amino acid sequence of a human TMD0986 as set forth in SEQ ID NO 153.

117. An isolated human TMD0986 polypeptide consisting essentially of amino acids 1-117 of a human TMD0986 as set forth in SEQ ID NO 153.

118. An isolated polypeptide which is human TMD0986 having 90% or more amino acid sequence identity to the amino acid sequence set forth in SEQ ID NO 153, and which has protein binding activity.

119. An antibody specific for an epitope selected from the polypeptide of claim 117.

120. A method of detecting an retinal cell, comprising:

contacting a sample comprising cells with a polynucleotide specific for NM_013941 (SEQ ID NO 181), or a naturally-occurring polymorphisms thereof, of claim 142 under conditions effective for said polynucleotide to hybridize specifically to said gene, and

detecting specific hybridization.

121. A method of claim 120, wherein said detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization.

122. A method of detecting an retinal cell, comprising:

contacting a sample comprising cells with a binding partner specific for a polypeptide coded for by NM_013941 (SEQ ID NO 182), or a naturally-occurring polymorphism thereof, of claim 142 under conditions effective for said binding partner bind specifically to said polypeptide, and

detecting specific binding.

123. A method of claim 122, wherein said detecting is performed by:

immunocytochemistry, immunoprecipitation, or Western blot.

124. A method of delivering an agent to a retinal cell, comprising:

contacting a retinal cell with an agent coupled to binding partner specific for by NM_013941 (SEQ ID NO 182), or naturally-occurring polymorphism thereof, of claim 142, whereby said agent is delivered to said cell.

125. A method of claim 124, wherein the agent is a therapeutic agent or an imaging agent.

126. A method of claim 124, wherein the agent is cytotoxic.

127. A method of claim 124, wherein the binding partner is an antibody.

128. A method of modulating a retinal cell, comprising:

contacting said cell with an agent effective to modulate NM_013941 (SEQ ID NO 181 or 182), or the biological activity of a polypeptide encoded thereby, of claim 142, whereby the retinal cell is modulated.

129. A method of diagnosing a retinal disease associated with abnormal gene expression, or determining a subject's susceptibility to such disease, comprising:

assessing the expression of NM_013941, a polymorphism thereof, or polypeptide encoded thereby, of claim 142 in a tissue sample comprising retinal cells.

130. A method of claim 129, wherein assessing is:

measuring expression levels of said gene, determining the genomic structure of said gene, determining the mRNA structure of transcripts from said gene, or measuring the expression levels of polypeptide coded for by said gene.

131. A method of claim 129, wherein said assessing detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR,

RACE PCR, or *in situ* hybridization, and

using a polynucleotide probe having a sequence selected from SEQ ID NOS 183 or 184, or a complement thereto.

132. A method of assessing a therapeutic or preventative intervention in a subject having an retinal disease, comprising,

determining the expression levels of NM_013941, a polymorphism thereof, or polypeptide encoded thereby, of claim 142 in a tissue sample comprising retinal cells.

133. A method of claim 132, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

134. A method for identifying an agent that modulates the expression of NM_013941 or the biological activity of a polypeptide encoded thereby, comprising,

contacting an retinal cell with a test agent under conditions effective for said test agent to modulate the expression of NM_013941 or a polymorphism thereof, of claim 142, or the biological activity of a polypeptide encoded thereby, in said retinal cell, and

determining whether said test agent modulates said gene or polypeptide.

135. A method of claim 134, wherein said agent is an antisense polynucleotide to a target polynucleotide sequence selected from SEQ ID NO 181 and which is effective to inhibit translation of said gene.

136. A method of detecting polymorphisms in NM_013941, comprising:

comparing the structure of: genomic DNA or RNA or cDNA comprising all or part of an allele of NM_013941, with SEQ ID NOS 181 or 182 of claim 142.

137. A method of claim 136, wherein said polymorphism is a nucleotide deletion, substitution, inversion, or transposition.

138. A non-human, transgenic mammal whose genome comprises a functional disruption of a gene represented by NM_013941 (SEQ ID NO 181) of claim 142, and which has a defect in

retinal function.

139. A mammalian retinal cell whose genome comprises a functional disruption of a gene represented by NM_013941 (SEQ ID NO 181) of claim 142, and which has a defect in retinal function.

140. A mammalian cell of claim 139, wherein said cell is a mouse cell.

141. A method of selecting a gene predominantly expressed in retinal cells from a database comprising polynucleotide sequences for genes, comprising:

displaying, in a computer-readable medium, a polynucleotide sequence or polypeptide sequence for NM_013941 (SEQ ID NO 181 or 182) of claim 142, or complements to the polynucleotides sequence,

wherein said displayed sequences have been retrieved from said database upon selection by a user.

142. A composition comprising:

a retinal specific gene consisting essentially of NM_013941 (SEQ ID NO 181 or 182), or a polypeptide encoded thereby.

143. A method of detecting a spleen cell, comprising:

contacting a sample comprising cells with a polynucleotide specific for TMD1030 (XM_166853) or TMD0621 (XM_166205) of claim 170 under conditions effective for said polynucleotide to hybridize specifically to said gene, and

detecting specific hybridization.

144. A method of claim 143, wherein said detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization.

145. A method of detecting a spleen cell, comprising:

contacting a sample comprising cells with a binding partner specific for a polypeptide

coded for by TMD1030 (XM_166853) or TMD0621 (XM_166205) of claim 170 under conditions effective for said binding partner bind specifically to said polypeptide, and detecting specific binding.

146. A method of claim 145, wherein said detecting is performed by: immunocytochemistry, immunoprecipitation, or Western blot.

147. A method of delivering an agent to a spleen cell, comprising: contacting a spleen with an agent coupled to binding partner specific for TMD1030 (XM_166853) or TMD0621 (XM_166205) of claim 170, whereby said agent is delivered to said cell.

148. A method of claim 147, wherein the agent is a therapeutic agent or an imaging agent.

149. A method of claim 148, wherein the agent is cytotoxic.

150. A method of claim 147, wherein the binding partner is an antibody.

151. A method of modulating a spleen, immune, or reticuloendothelial cell, comprising: contacting said cell with an agent effective to modulate TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), or the biological activity of a polypeptide encoded thereby, of claim 170, whereby the cell is modulated.

152. A method of assessing spleen function, comprising: detecting a polypeptide coded for by TMD1030 (XM_166853) or TMD0621 (XM_166205) of claim 170, or fragments thereof, in a body fluid, whereby the amount of said polypeptide in said fluid is a measure of spleen function.

153. A method of claim 152, wherein said detecting is performed using an antibody which is specific for said polypeptide.

154. A method of claim 152, wherein said detecting is performed by RIA, ELISA, or Western blot.

155. A method of expressing a heterologous polynucleotide in spleen cells, comprising:

expressing a nucleic acid construct in spleen cell, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is SEQ ID NO 205-213.

156. A method of assessing a therapeutic or preventative intervention in a subject having a spleen or lymphoid disease, comprising,

determining the expression levels of TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), or a polypeptide encoded thereby, of claim 170 in a tissue sample comprising spleen, lymphoid, or reticuloendothelial cells.

157. A method of claim 156, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

158. A method for identifying an agent that modulates the expression of TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), comprising,

contacting a spleen, lymphoid, or reticuloendothelial cell, with a test agent under conditions effective for said test agent to modulate the expression of TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), of claim 170, and

determining whether said test agent modulates said gene.

159. A method of claim 158, wherein said agent is an antisense which is effective to inhibit translation of said gene.

160. A method for identifying an agent that modulates the expression of a polypeptide coded for by TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), comprising,

contacting a polypeptide coded for by TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205) of claim 170, with a test agent under conditions effective for said test agent to modulate said polypeptide, and

determining whether said test agent modulates said polypeptide.

161. A method of detecting polymorphisms in comprising, comparing the structure of :

genomic DNA or RNA or cDNA comprising all or part of an allele of TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205), with SEQ ID NOS 185, 187, 189, or 191 of claim 170.

162. A method of claim 161, wherein said polymorphism is a nucleotide deletion, substitution, inversion, or transposition.

163. A method of identifying a genetic basis for a spleen, lymphoid, and/or reticuloendothelial disease or disease-susceptibility, comprising: determining the association of a spleen, lymphoid, and/or reticuloendothelial disease or disease-susceptibility with a nucleotide sequence present in the gene complex of claim 170.

164. A method of claim 163, wherein determining is performed by producing a human-linkage map of said complex.

~~165. A method~~ of claim 163, ~~wherein~~ determining is performed by comparing the nucleotide sequences between normal subjects and subjects having a spleen, lymphoid, and/or reticuloendothelial disease.

166. A non-human, transgenic mammal, or a cell thereof. whose genome comprises a functional disruption of a gene represented by TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205) of claim 170, and

which has a defect in spleen, lymphoid, and/or reticuloendothelial disease function.

167. A mammalian cell of claim 166, wherein said cell is a mouse cell.

168. A spleen, lymphoid, and/or reticuloendothelial cell, comprising a gene operatively linked to an expression control sequence effective to express said gene in spleen, lymphoid, and/or reticuloendothelial, wherein said sequence is SEQ ID NO 205-213.

169. A method of selecting a gene predominantly expressed in spleen, lymphoid, and/or reticuloendothelial cells from a database comprising polynucleotide sequences for genes, comprising:

displaying, in a computer-readable medium, a polynucleotide sequence or polypeptide sequence for TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), or TMD0621 (XM_166205) of claim 170, or complements to the polynucleotides sequence, wherein said displayed sequences have been retrieved from said database upon selection by a user.

170. A composition consisting essentially of the 11q12.2 spleen gene complex, comprising TMD1030 (XM_166853), TMD1029 (XM_166854), TMD1028 (XM_166855), and TMD0621 (XM_166205).

171. A composition of claim 170, wherein said complex consists essentially of the chromosome region between STS markers G62658 and SHGC-154002.

172. A method of detecting a pancreas cell, comprising:

contacting a sample comprising cells with a polynucleotide specific TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127 of claim 199 under conditions effective for said polynucleotide to hybridize specifically to said gene, and

detecting specific hybridization.

173. A method of claim 172, wherein said detecting is performed by:

Northern blot analysis, polymerase chain reaction (PCR), reverse transcriptase PCR, RACE PCR, or *in situ* hybridization.

174. A method of detecting a pancreas cell, comprising:

contacting a sample comprising cells with a binding partner specific for a polypeptide coded for by TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127

of claim 199 under conditions effective for said binding partner bind specifically to said polypeptide, and

detecting specific binding.

175. A method of claim 174, wherein said detecting is performed by:

immunocytochemistry, immunoprecipitation, or Western blot.

176. A method of delivering an agent to a pancreas cell, comprising:

contacting a pancreas with an agent coupled to binding partner specific for TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127 of claim 199, whereby said agent is delivered to said cell.

177. A method of claim 176, wherein the agent is a therapeutic agent or an imaging agent.

178. A method of claim 176, wherein the agent is cytotoxic.

179. A method of claim 176, wherein the binding partner is an antibody.

180. A method of modulating a pancreas, immune, or reticuloendothelial cell, comprising:

contacting said cell with an agent effective to modulate TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127, or the biological activity of a polypeptide encoded thereby, of claim 199, whereby the cell is modulated.

181. A method of assessing pancreas function, comprising:

detecting a polypeptide coded for by TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127 of claim 199, or fragments thereof, in a body fluid, whereby the amount of said polypeptide in said fluid is a measure of pancreas function.

182. A method of claim 181, wherein said detecting is performed using an antibody which is specific for said polypeptide.

183. A method of claim 181, wherein said detecting is performed by RIA, ELISA, or Western blot.

184. A method of expressing a heterologous polynucleotide in pancreas cells, comprising:

expressing a nucleic acid construct in pancreas cell, said construct comprising a promoter sequence operably linked to said heterologous polynucleotide, wherein said promoter sequence is selected SEQ ID NO 258, 261, 262, 265-267, 270-272, 275, 278, 279, 282-284, 287, 290-293, 296, 297, 300, 303, 306, 309-314, 317-320, 323-326, 329, 332-333, 336-338, 341, and 344.

185. A method of assessing a therapeutic or preventative intervention in a subject having a pancreas or lymphoid disease, comprising,

determining the expression levels of TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127, or a polypeptide encoded thereby, of claim 199 in

a tissue sample comprising pancreas, lymphoid, or reticuloendothelial cells.

186. A method of claim 185, further comprising assessing the expression levels of a plurality of said genes or polypeptides.

187. A method for identifying an agent that modulates the expression of TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127, comprising,

contacting a pancreas, lymphoid, or reticuloendothelial cell, with a test agent under conditions effective for said test agent to modulate the expression of TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127, of claim 199, and

determining whether said test agent modulates said gene.

188. A method of claim 187, wherein said agent is an antisense which is effective to inhibit translation of said gene.

189. A method for identifying an agent that modulates the expression of a polypeptide coded for by TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127, comprising,

contacting a polypeptide coded for by TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127 of claim 199, with a test agent under conditions effective for said test agent to modulate said polypeptide, and

determining whether said test agent modulates said polypeptide.

190. A method of claim 189, wherein said test agent is an antibody.

191. A method of detecting polymorphisms in comprising, comparing the structure of : genomic DNA or RNA or cDNA comprising all or part of an allele of TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127, with SEQ ID NOS of Table 23 of claim 199.

192. A method of claim 191, wherein said polymorphism is a nucleotide deletion, substitution, inversion, or transposition.

193. A method of identifying a genetic basis for a pancreas disease or disease-susceptibility, comprising: determining the association of a pancreas disease or disease-susceptibility with a gene of claim 199.

194. A method of claim 193, wherein determining is performed by producing a human-linkage map of said gene.

195. A method of claim 193, wherein determining is performed by comparing the nucleotide sequences between normal subjects and subjects having a pancreas disease.

196. A non-human, transgenic mammal, or a cell thereof. whose genome comprises a functional disruption of a gene represented by TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127, of claim 199, and which has a defect in pancreas, lymphoid, and/or reticuloendothelial disease function.

197. A mammalian cell of claim 196, wherein said cell is a mouse cell.

198. A method of selecting a gene predominantly expressed in pancreas tissue from a

database comprising polynucleotide and amino acid sequences for genes, comprising:

displaying, in a computer-readable medium, a polynucleotide sequence or polypeptide sequence for TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127, of claim 199, or complements to the polynucleotides sequence, wherein said displayed sequences have been retrieved from said database upon selection by a user.

199. A composition comprising genes and/or polypeptide which are expressed predominantly in pancreas tissue comprising:

TMD0077, TMD0233, TMD0256, TMD0258, TMD0267, TMD0271, TMD0290, TMD0530, TMD0574, TMD0608, TMD0639, TMD0645, TMD0674, TMD0675, TMD0677, TMD0726, TMD0727, TMD0739, TMD0753, TMD1111, and/or TMD1127.

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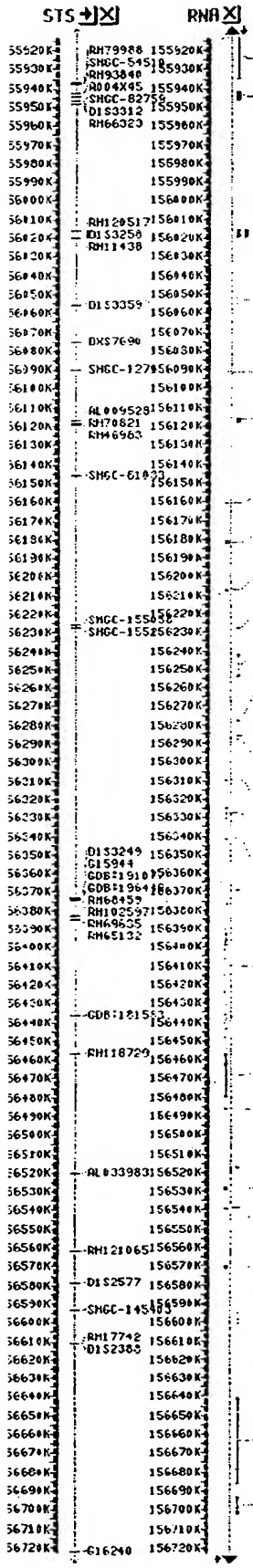

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XM_086610	CD1D	
XM_048792	CD1A	
NM_001765.1	CD1C	
NM_001764.1	CD1B	
NM_030893.1	CD1E	
XM_060945	LOC128360	TMD0024
XM_060946	LOC128361	TMD1779
XM_060947	LOC128362	TMD0884
XM_060948	LOC128363	TMD0025
XM_089422	LOC164169	TMD1780
XM_089421	LOC149631	TMD1781
XM_060949	LOC128364	
XM_089420	LOC164168	
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Fig. 1

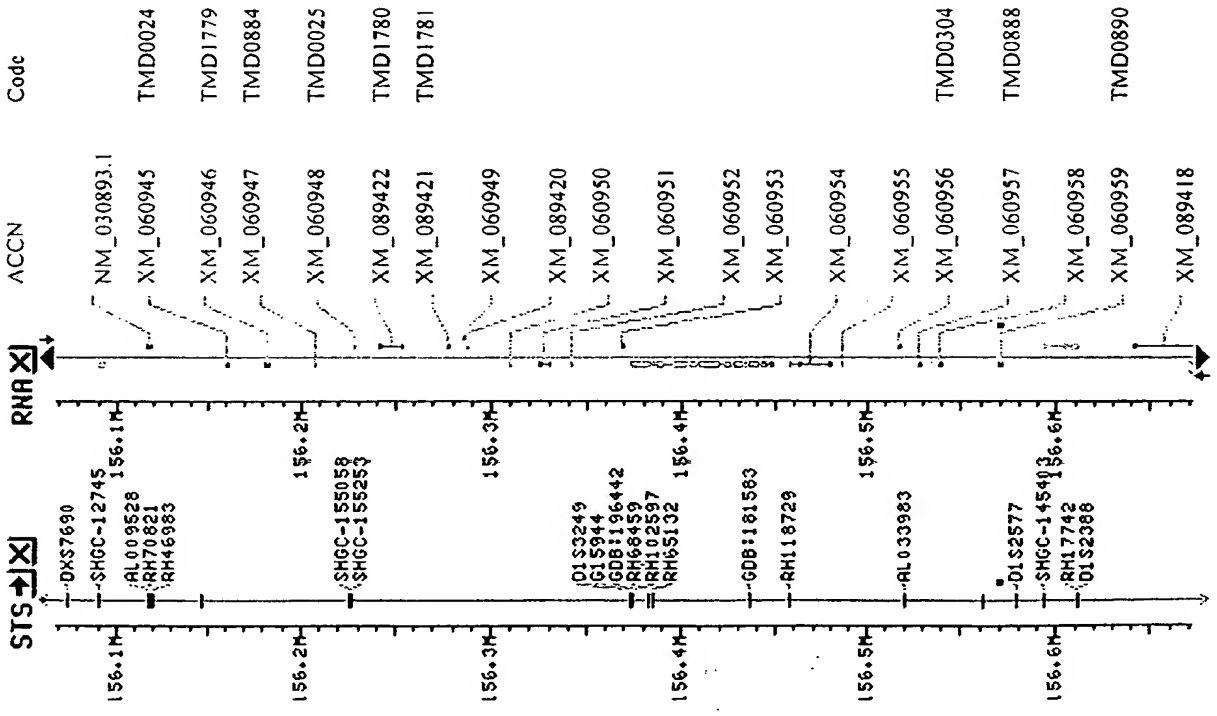
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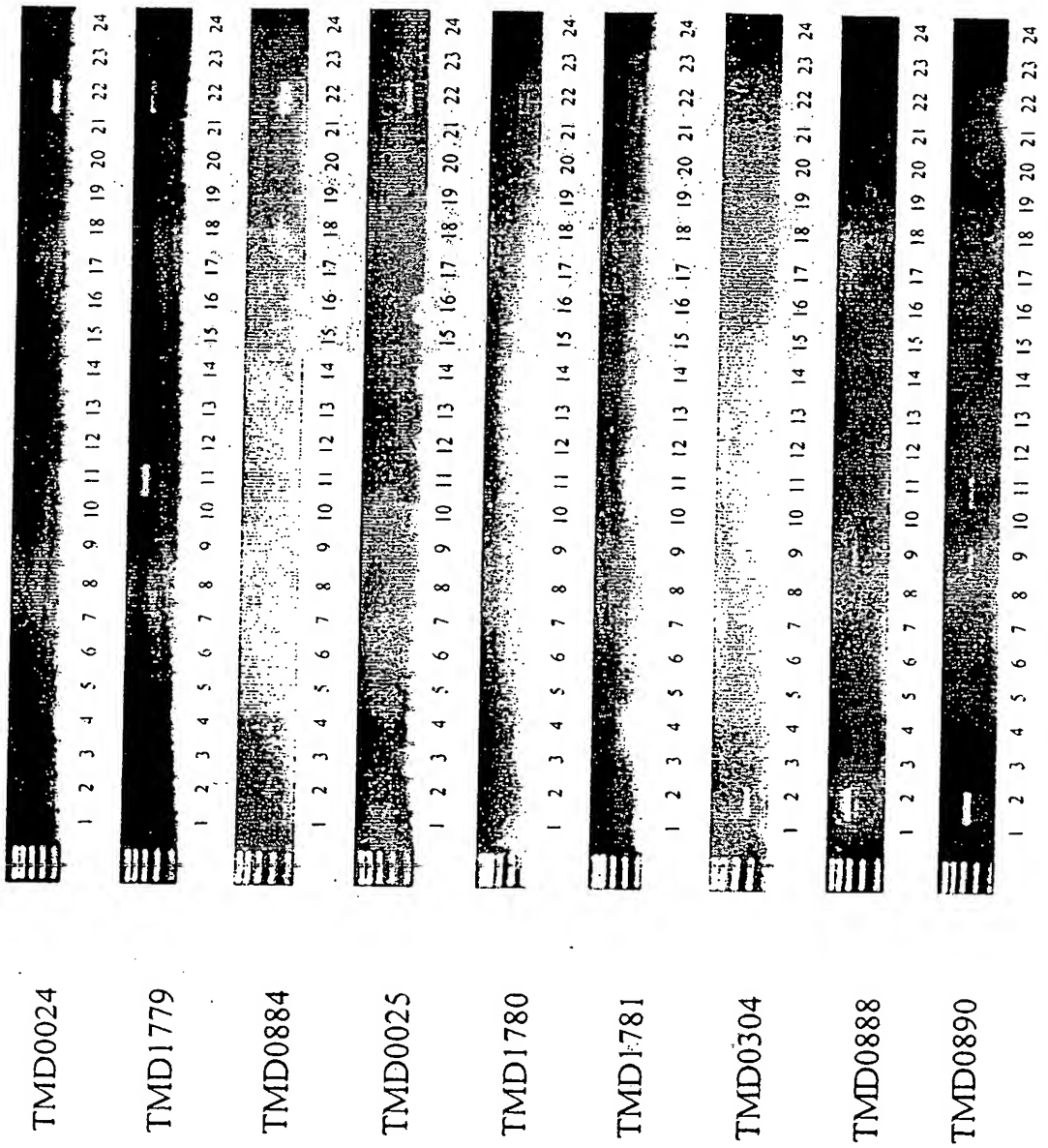
Fig. 2



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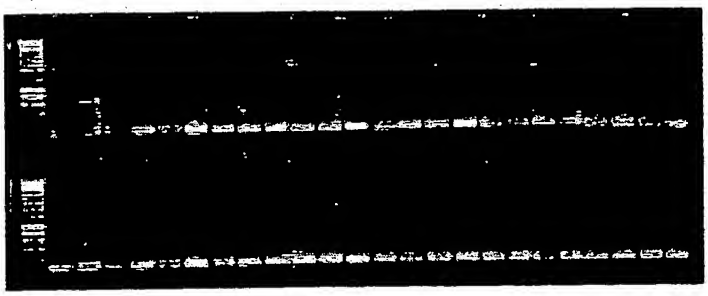

FIG. 4

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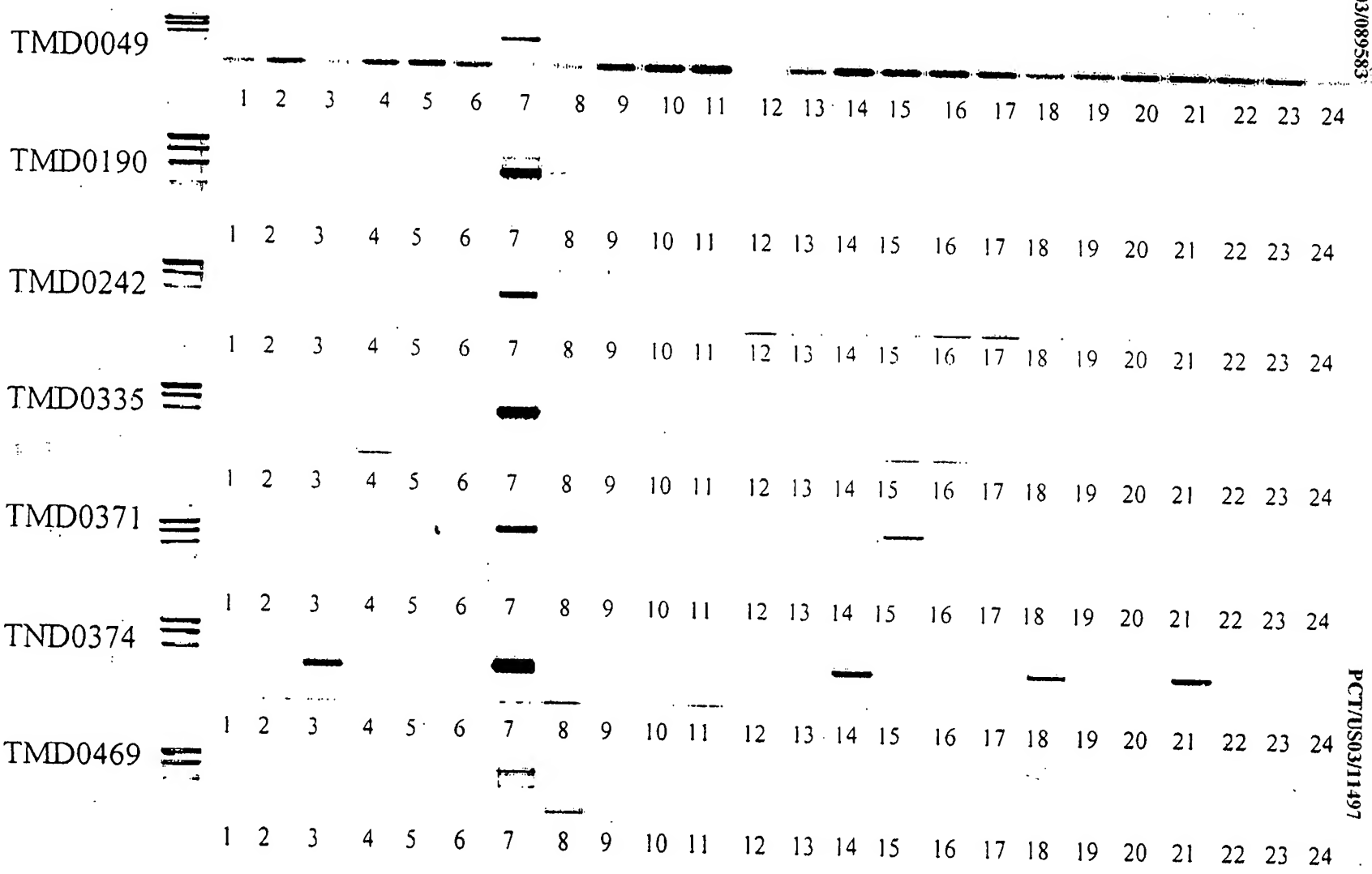

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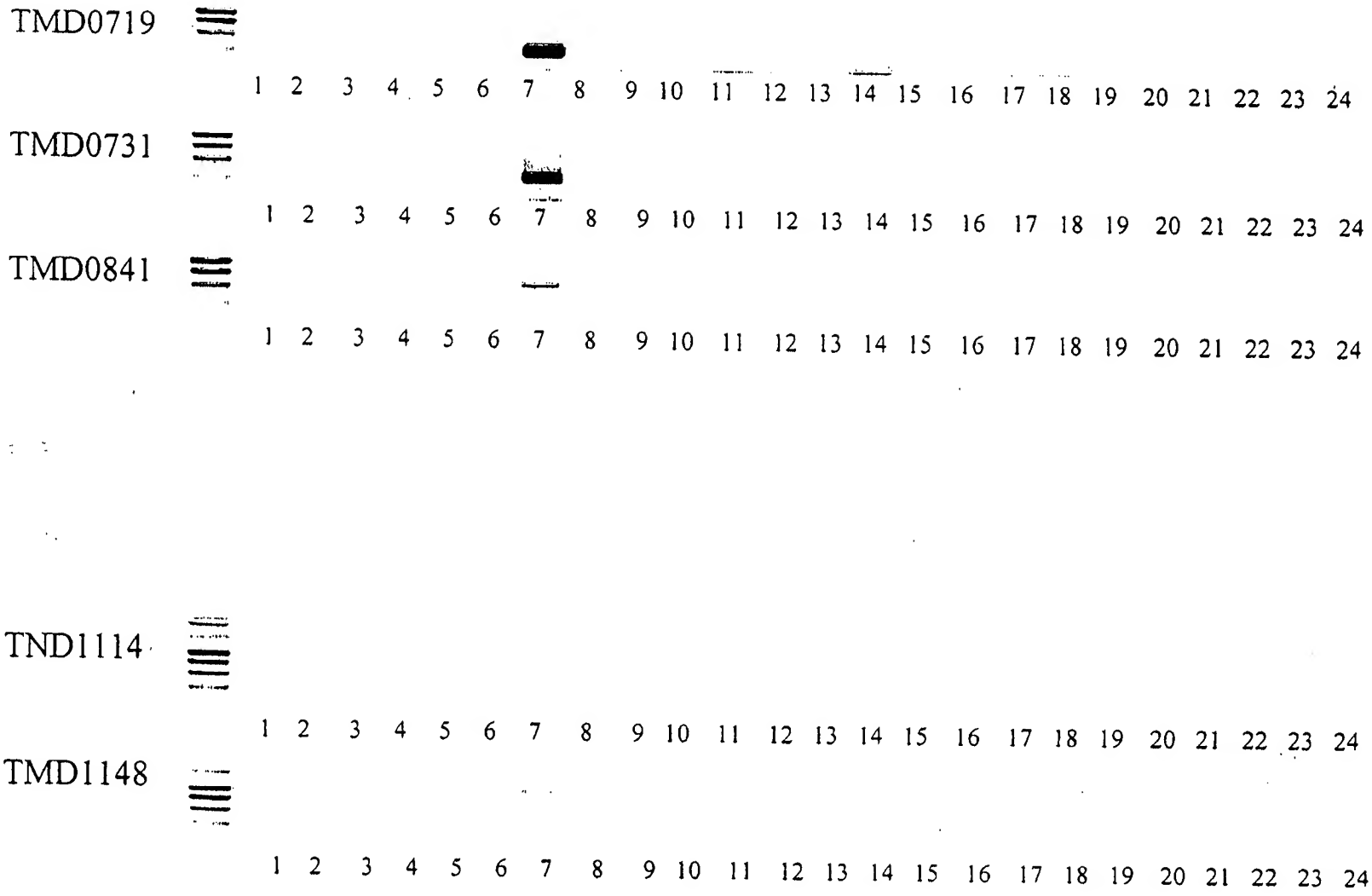

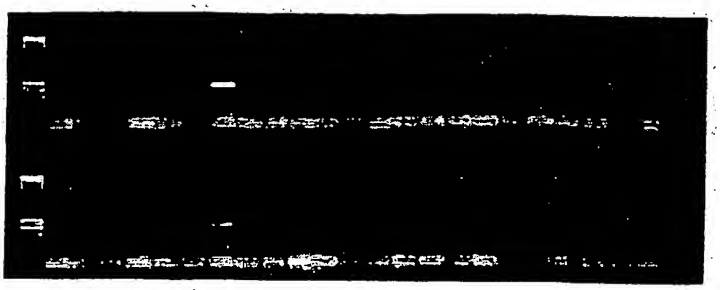

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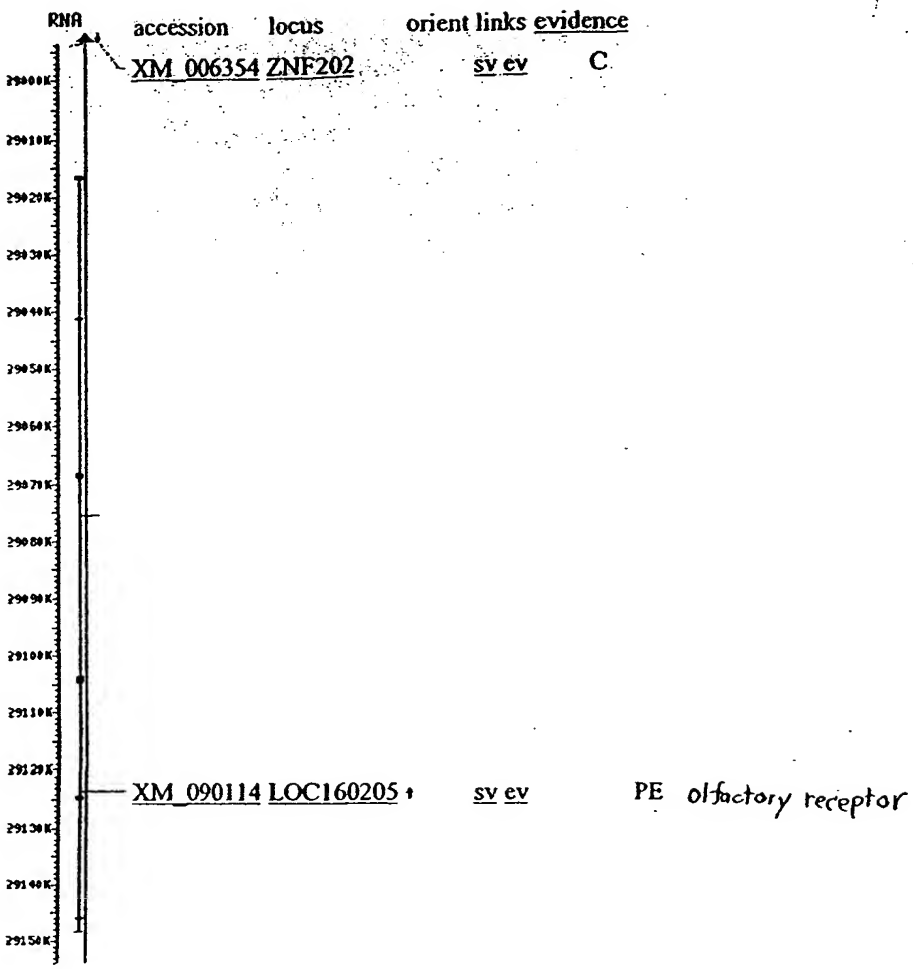
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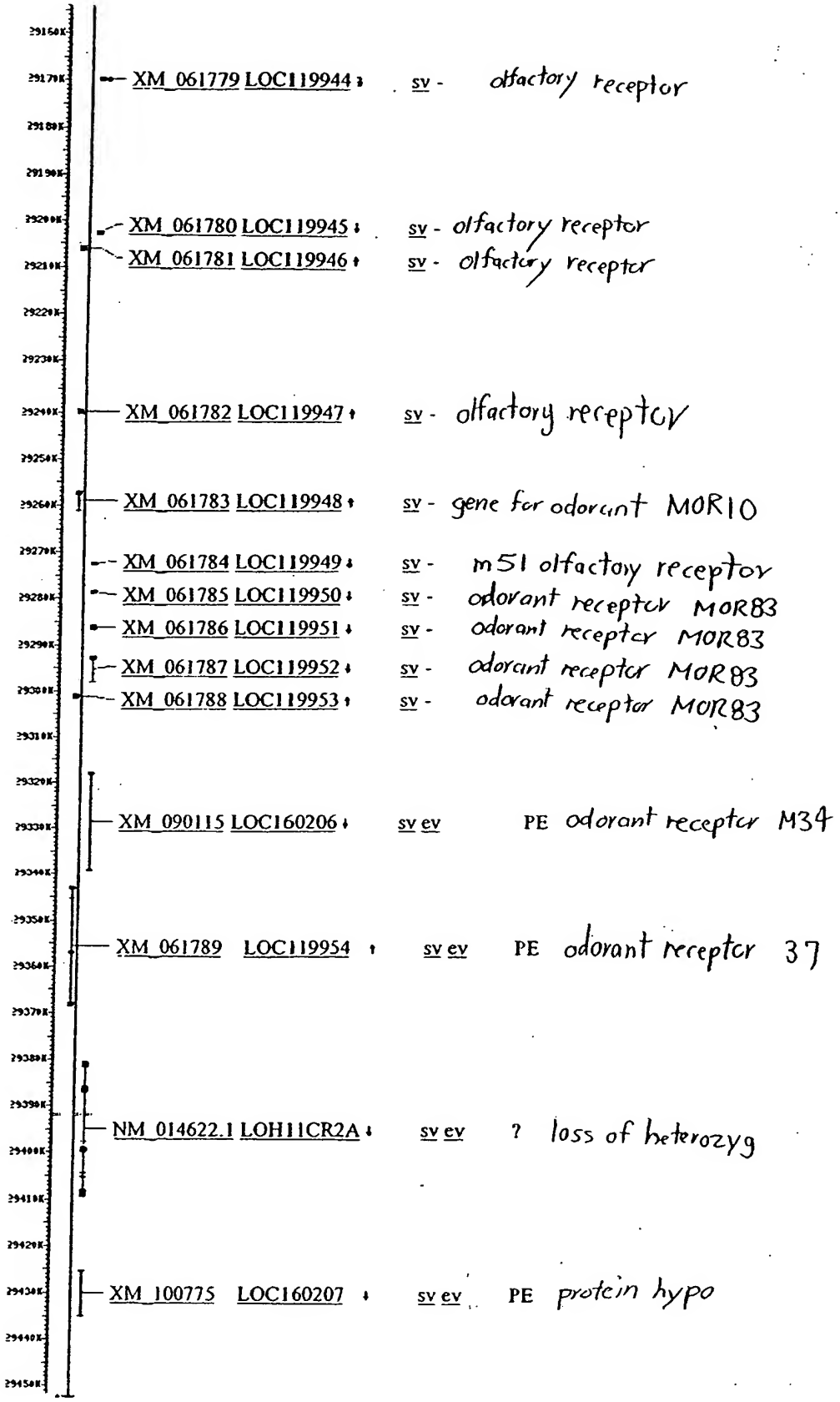
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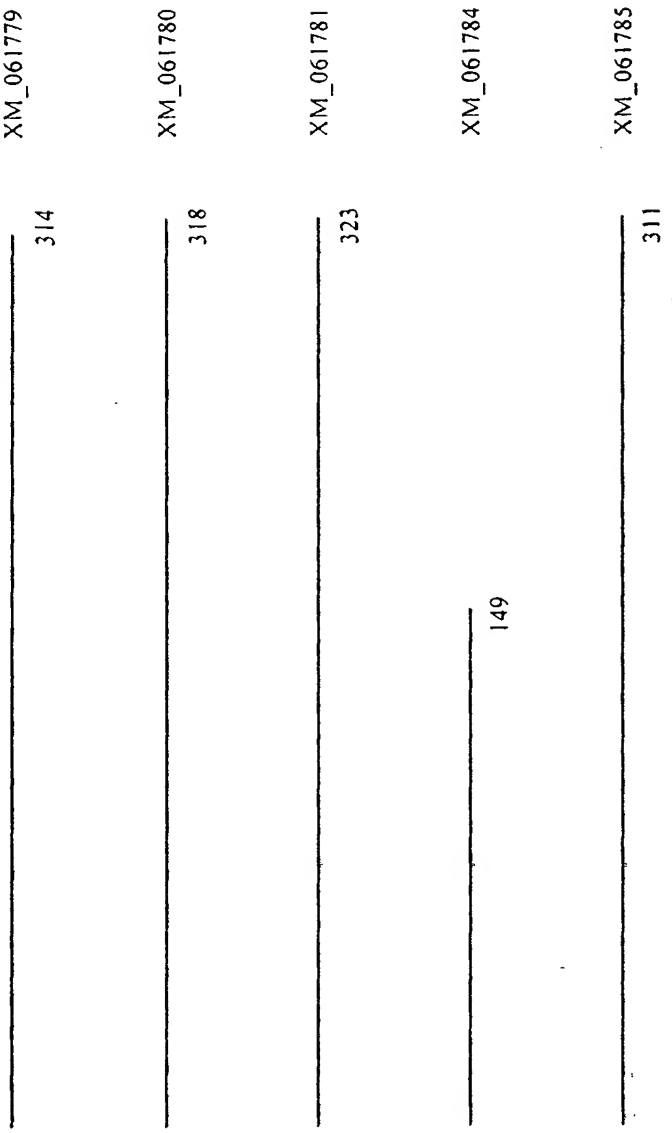
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Fig. 8

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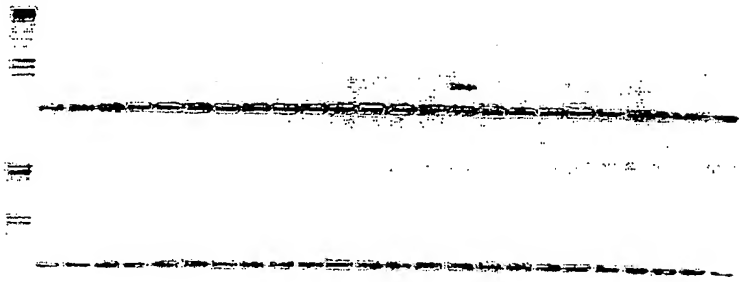

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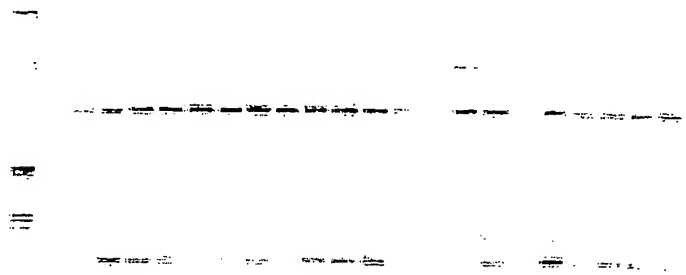

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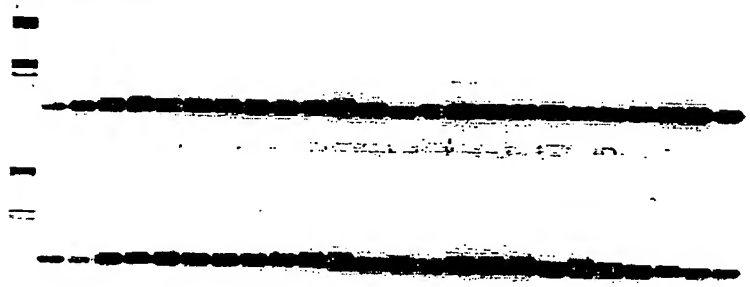

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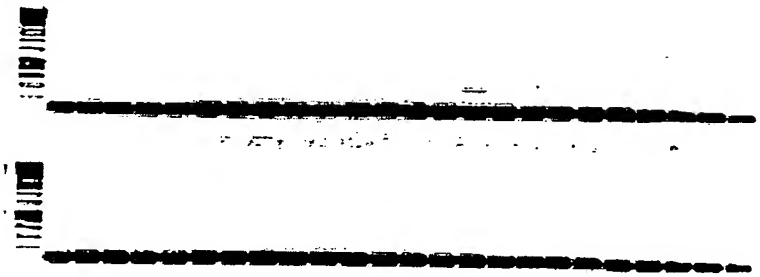

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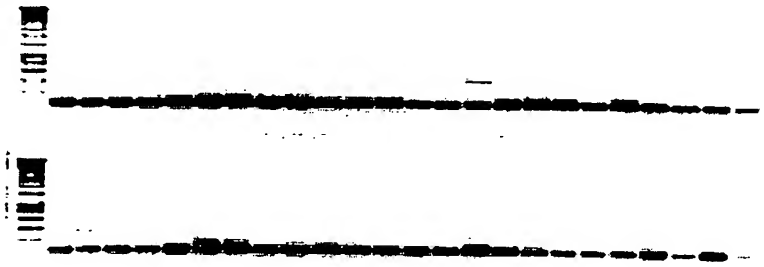

Fig. 9B

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TMD0621
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Fig.10

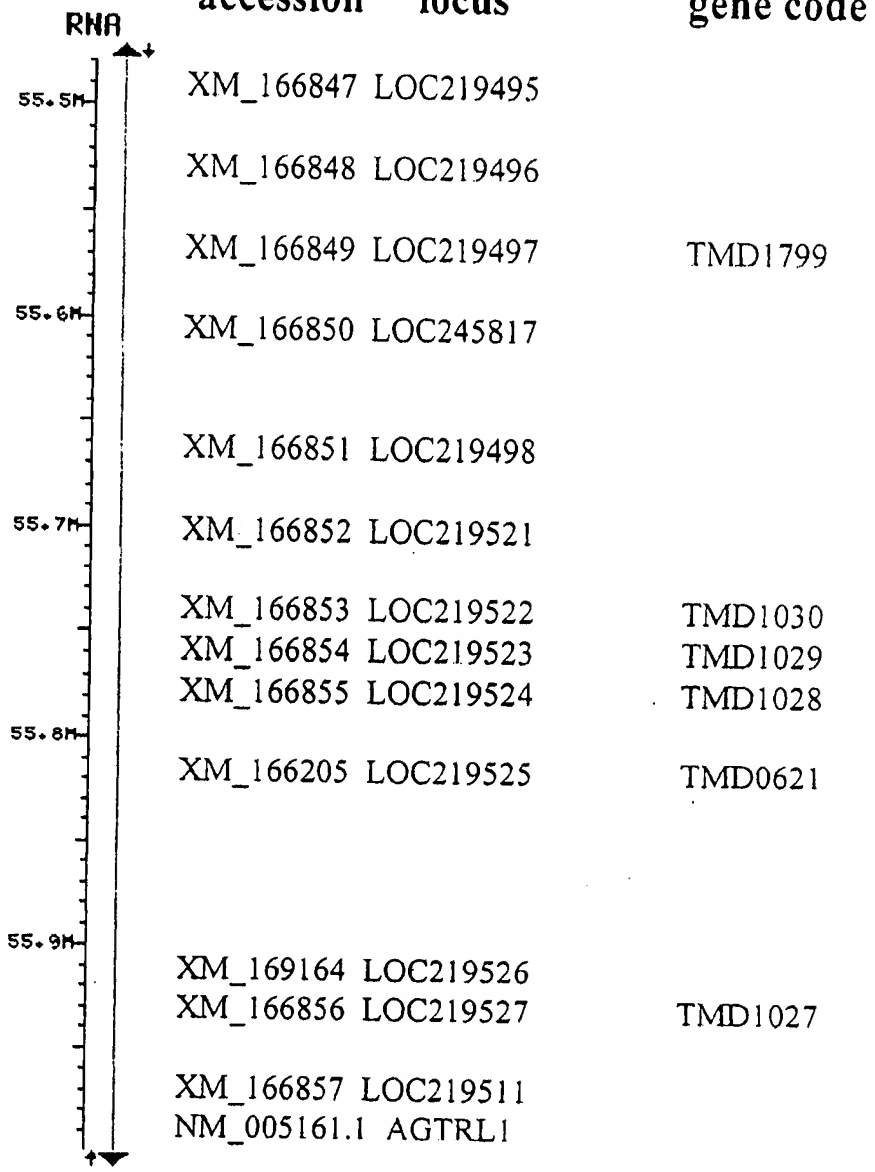
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Fig. 11

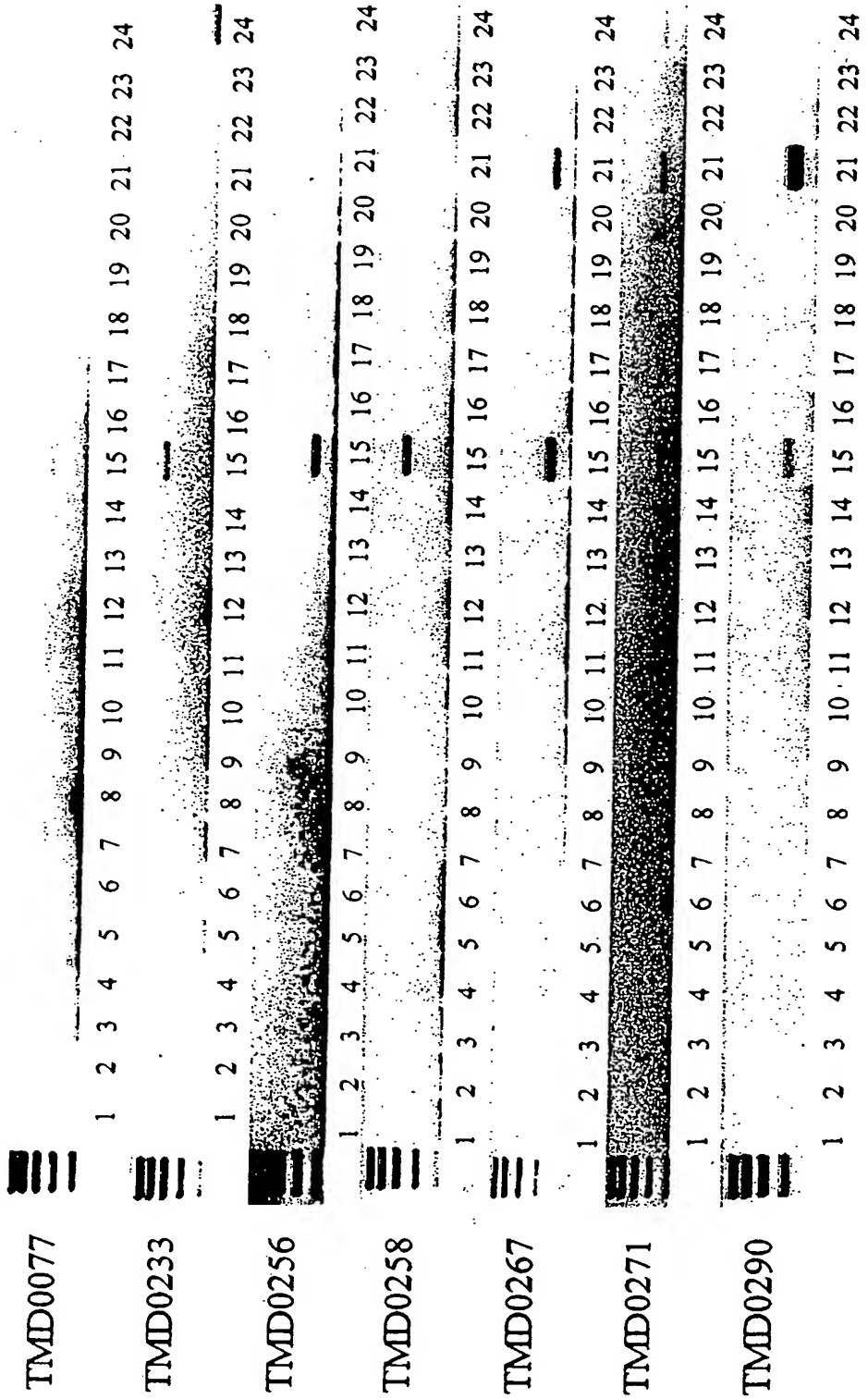

FIG. 12A

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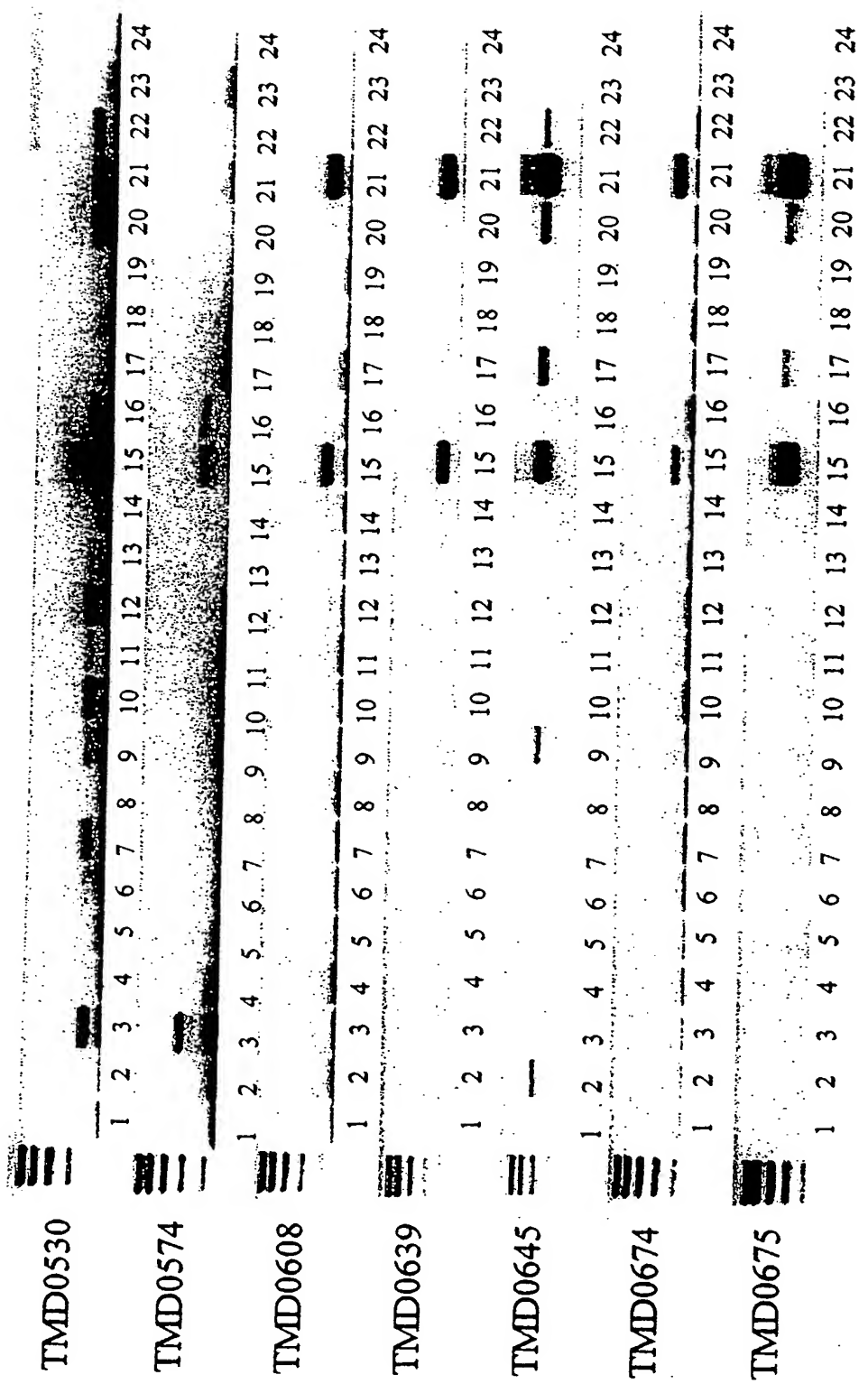
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FIG. 12B

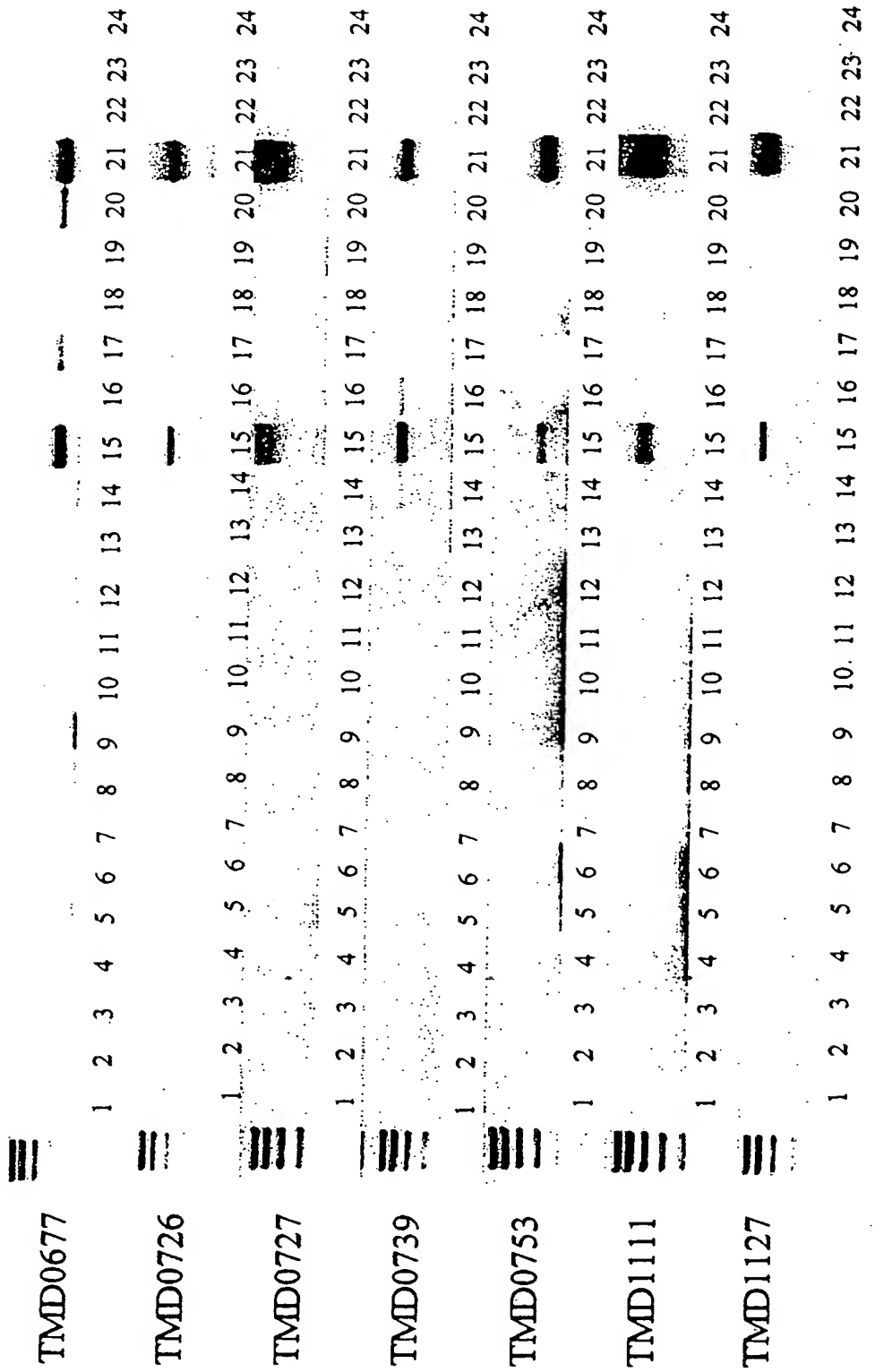
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FIG. 12C

16U 200 PCT FINAL.ST25

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Phe Ser Ser Leu Ala Arg Leu Gln Gln Leu Leu Phe Val Ile Phe Leu
            20                  25                  30

ctc ctc tac ctg ttc act ctg ggc acc aat gca atc atc att tcc acc      144
Leu Leu Tyr Leu Phe Thr Leu Gly Thr Asn Ala Ile Ile Ser Thr
        35                  40                  45

att gtc ctg gac agg gcc ctt cat atc ccc atg tac ttc ttc ctt gcc      192
Ile Val Leu Asp Arg Ala Leu His Ile Pro Met Tyr Phe Phe Leu Ala
    50                  55                  60

atc ctc tct tgc tct gag att tgc tac acc ttc atc att gta ccc aag      240
Ile Leu Ser Cys Ser Glu Ile Cys Tyr Thr Phe Ile Ile Val Pro Lys
65                  70                  75                  80

atg ctg gtt gac ctg ctg tcc cag aag aag acc att tct ttc ctg ggc      288
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                85                  90                  95

tgt gcc atc caa atg ttt tcc ttc ctc ttc ctt ggc tgc tct cac tcc      336
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            100                 105                 110

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        115                 120                 125

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tcc ttg gta ttt cac ctg cct ttt tat tcc tcc aat caa cta cat cac      528
Ser Leu Val Phe His Leu Pro Phe Tyr Ser Ser Asn Gln Leu His His
                165                 170                 175

ttc ttc tgt gac att gct cct gtc ctc aag ctg gca tct cac cat aac      576
Phe Phe Cys Asp Ile Ala Pro Val Leu Lys Leu Ala Ser His His Asn
            180                 185                 190

cac ttt agt cag att gtc atc ttc atg ctc tgt aca ttg gtc ctg gct      624
His Phe Ser Gln Ile Val Ile Phe Met Leu Cys Thr Leu Val Leu Ala
        195                 200                 205

atc ccc tta ttg ttg atc ttg gtg tcc tat gtt cac atc ctc tct gcc      672
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    210                 215                 220

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Ile Leu Gln Phe Pro Ser Thr Leu Gly Val Ile Ala Lys Arg Lys Phe
225                 230                 235                 240

cac aat agt gat gat ttc tca cat tat aac tct ttt caa gat cca cct      768
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        35                  40                  45

Ile Val Leu Asp Arg Ala Leu His Ile Pro Met Tyr Phe Phe Leu Ala
    50                  55                  60

Ile Leu Ser Cys Ser Glu Ile Cys Tyr Thr Phe Ile Ile Val Pro Lys
65                  70                  75                  80

Met Leu Val Asp Leu Leu Ser Gln Lys Lys Thr Ile Ser Phe Leu Gly
                85                  90                  95

Cys Ala Ile Gln Met Phe Ser Phe Leu Phe Leu Gly Cys Ser His Ser
            100                 105                 110

Phe Leu Leu Ala Val Met Gly Tyr Asp Arg Tyr Ile Ala Ile Cys Asn
        115                 120                 125

Pro Leu Arg Tyr Ser Val Leu Met Gly His Gly Val Cys Met Gly Leu
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Val Ala Ala Ala Cys Ala Cys Gly Phe Thr Val Ala Gln Ile Ile Thr
145                 150                 155                 160
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                165                 170                 175

Phe Phe Cys Asp Ile Ala Pro Val Leu Lys Leu Ala Ser His His Asn
            180                 185                 190

His Phe Ser Gln Ile Val Ile Phe Met Leu Cys Thr Leu Val Leu Ala
        195                 200                 205

Ile Pro Leu Leu Leu Ile Leu Val Ser Tyr Val His Ile Leu Ser Ala
    210                 215                 220

Ile Leu Gln Phe Pro Ser Thr Leu Gly Val Ile Ala Lys Arg Lys Phe
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His Asn Ser Asp Asp Phe Ser His Tyr Asn Ser Phe Gln Asp Pro Pro
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Val Asn Lys Ser Leu Leu Ile Asp
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Phe Leu Phe Ile Leu Ser Phe Ser Glu Ser Cys Tyr Thr Phe Val Ile
            20                  25                  30

atc cct cag ctg ctg gtc cac ctg ctc tca gac acc aag acc atc tcc      144
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acc aac tgc ctc ctc att gct gtg atg gga tat gat cgc tat gta gca      240
Thr Asn Cys Leu Leu Ile Ala Val Met Gly Tyr Asp Arg Tyr Val Ala
65                  70                  75                  80

att tgt cac cct ctg agg tac aca ctc atc ata aac aaa agg ctg ggg      288
Ile Cys His Pro Leu Arg Tyr Thr Leu Ile Ile Asn Lys Arg Leu Gly
                85                  90                  95

ttg gag ttg att tct ctc tca gga gcc aca ggt ttc ttt att gct ttg      336
Leu Glu Leu Ile Ser Leu Ser Gly Ala Thr Gly Phe Phe Ile Ala Leu
            100                 105                 110

gtg gcc acc aac ctc att tgt gac atg cgt ttt tgt ggc ccc aac agg      384
Val Ala Thr Asn Leu Ile Cys Asp Met Arg Phe Cys Gly Pro Asn Arg
        115                 120                 125

gtt aac cac tat ttc tgt gac atg gca cct gtt atc aag tta gcc tgc      432
Val Asn His Tyr Phe Cys Asp Met Ala Pro Val Ile Lys Leu Ala Cys
    130                 135                 140

act gac acc cat gtg aaa gag ctg gct tta ttt agc ctc agc atc ctg      480
Thr Asp Thr His Val Lys Glu Leu Ala Leu Phe Ser Leu Ser Ile Leu
145                 150                 155                 160

gta att atg gtg cct ttt ctg tta att ctc ata tcc tat ggc ttc ata      528
Val Ile Met Val Pro Phe Leu Leu Ile Leu Ile Ser Tyr Gly Phe Ile
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Ala Ser Ile Ile Tyr Leu Arg Pro Lys Ser Lys Ser Ala Ser Asp Lys
    210                 215                 220

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Asp Gln Leu Val Ala Val Thr Tyr Thr Val Val Thr Pro Leu Leu Asn
225                 230                 235                 240

cct ctt gtc tac agt ctg agg aac aaa gag gta aaa act gca ttg aaa      768
Pro Leu Val Tyr Ser Leu Arg Asn Lys Glu Val Lys Thr Ala Leu Lys
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Ile Pro Gln Leu Leu Val His Leu Leu Ser Asp Thr Lys Thr Ile Ser
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            100                 105                 110

Val Ala Thr Asn Leu Ile Cys Asp Met Arg Phe Cys Gly Pro Asn Arg
        115                 120                 125

Val Asn His Tyr Phe Cys Asp Met Ala Pro Val Ile Lys Leu Ala Cys
    130                 135                 140

Thr Asp Thr His Val Lys Glu Leu Ala Leu Phe Ser Leu Ser Ile Leu
145                 150                 155                 160

Val Ile Met Val Pro Phe Leu Leu Ile Leu Ile Ser Tyr Gly Phe Ile
                165                 170                 175

Val Asn Thr Ile Leu Lys Ile Pro Ser Ala Glu Gly Lys Lys Ala Phe
            180                 185                 190

Val Thr Cys Ala Ser His Leu Thr Val Val Phe Val His Tyr Gly Cys
        195                 200                 205

Ala Ser Ile Ile Tyr Leu Arg Pro Lys Ser Lys Ser Ala Ser Asp Lys
    210                 215                 220

Asp Gln Leu Val Ala Val Thr Tyr Thr Val Val Thr Pro Leu Leu Asn
225                 230                 235                 240

Pro Leu Val Tyr Ser Leu Arg Asn Lys Glu Val Lys Thr Ala Leu Lys
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ctttctgtat ataaaaacat ataactaata cacacacact catacacaaa tatcaatgga 300

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tagtaacttc agaagtatat aaatgaagac tggataccag caagacatac tggatgattt 660

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ttcgttctat attctgatca gcttcaggta gctgaagtta acgttttcca ctttggagag 1680

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acctctgtcc ctgactctcc tttatagaag tgctctcc atg gag caa gtc aat aag    2036
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Thr Val Val Arg Glu Phe Val Val Leu Gly Phe Ser Ser Leu Ala Arg
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Leu Gln Gln Leu Leu Phe Val Ile Phe Leu Leu Leu Tyr Leu Phe Thr
        25                  30                  35

ctg ggc acc aat gca atc atc att tcc acc att gtg ctg gac aga gcc      2180
Leu Gly Thr Asn Ala Ile Ile Ile Ser Thr Ile Val Leu Asp Arg Ala
    40                  45                  50

ctt cat act ccc atg tac ttc ttc ctt gcc atc ctt tct tgc tct gag      2228
Leu His Thr Pro Met Tyr Phe Phe Leu Ala Ile Leu Ser Cys Ser Glu
55                  60                  65                  70

att tgc tat acc ttt gtc att gta ccc aag atg ctg gtt gac ctg ctg      2276
Ile Cys Tyr Thr Phe Val Ile Val Pro Lys Met Leu Val Asp Leu Leu
                75                  80                  85

tcc cag aag aag acc att tct ttc ctg ggc tgt gcc atc caa atg ttt      2324
Ser Gln Lys Lys Thr Ile Ser Phe Leu Gly Cys Ala Ile Gln Met Phe
            90                  95                  100

tcc ttc ctc ttc ttt ggc tcc tct cac tcc ttc ctg ctg gca gcc atg      2372
Ser Phe Leu Phe Phe Gly Ser Ser His Ser Phe Leu Leu Ala Ala Met
        105                 110                 115

ggc tat gat cgc tat atg gcc atc tgt aac cca ctg cgc tac tca gtg      2420
Gly Tyr Asp Arg Tyr Met Ala Ile Cys Asn Pro Leu Arg Tyr Ser Val
    120                 125                 130

ctc atg gga cat ggg gtg tgt atg gga cta atg gct gct gcc tgt gcc      2468
Leu Met Gly His Gly Val Cys Met Gly Leu Met Ala Ala Ala Cys Ala
135                 140                 145                 150

tgt ggc ttc act gtc tcc ctg gtc acc acc tcc cta gta ttt cat ctg      2516
Cys Gly Phe Thr Val Ser Leu Val Thr Thr Ser Leu Val Phe His Leu
                155                 160                 165

ccc ttc cac tcc tcc aac cag ctc cat cac ttc ttc tgt gac atc tcc      2564
Pro Phe His Ser Ser Asn Gln Leu His His Phe Phe Cys Asp Ile Ser
            170                 175                 180

cct gtc ctt aaa ctg gca tct cag cac tcc ggc ttc agt cag ctg gtc      2612
Pro Val Leu Lys Leu Ala Ser Gln His Ser Gly Phe Ser Gln Leu Val
        185                 190                 195

ata ttc atg ctt ggt gta ttt gcc ttg gtc att cct ctg cta ctt atc      2660
Ile Phe Met Leu Gly Val Phe Ala Leu Val Ile Pro Leu Leu Leu Ile
    200                 205                 210

cta gtc tcc tac atc cgc atc atc tct gcc att cta aaa atc cct tcc      2708
Leu Val Ser Tyr Ile Arg Ile Ile Ser Ala Ile Leu Lys Ile Pro Ser
215                 220                 225                 230

tcc gtt gga aga tac aag acc ttc tcc acc tgt gcc tcc cat ctc att      2756
Ser Val Gly Arg Tyr Lys Thr Phe Ser Thr Cys Ala Ser His Leu Ile
                235                 240                 245

gtg gta act gtt cac tac agt tgt gcc tct ttc atc tac tta agg ccc      2804
Val Val Thr Val His Tyr Ser Cys Ala Ser Phe Ile Tyr Leu Arg Pro
            250                 255                 260

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Lys Thr Asn Tyr Thr Ser Ser Gln Asp Thr Leu Ile Ser Val Ser Tyr
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265 270 275

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Thr Ile Leu Thr Pro Leu Phe Asn Pro Met Ile Tyr Ser Leu Arg Asn
280 285 290

aag gaa ttc aaa tca gcc cta cga aga aca atc ggc caa act ttc tat 2948
Lys Glu Phe Lys Ser Ala Leu Arg Arg Thr Ile Gly Gln Thr Phe Tyr
295 300 305 310

cct ctt agt taa agagctattt tttaaactac taatgcctag tacatgccag 3000
Pro Leu Ser

gcagaacgtg tgttttatac attttttttc atttaattgt ccagctccac tgtaacataa 3060

gaacatttta catatgagaa gaatgaggct cacagaagtt aagacagtct ggctttctac 3120

tctccatgat actttaacaa gactaatcag atatgggaac agagcacaca gttccataac 3180

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caaaggatat gaacagacac ttctcaaaag aagacattta tgcagccaga aaacacatga 4860

aaaaatgctc atcactggcc atcagagaaa tgcaaatcaa aaccacaatg agataccatc 4920

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Leu Leu Tyr Leu Phe Thr Leu Gly Thr Asn Ala Ile Ile Ile Ser Thr
35 40 45

Ile Val Leu Asp Arg Ala Leu His Thr Pro Met Tyr Phe Phe Leu Ala
50 55 60

Ile Leu Ser Cys Ser Glu Ile Cys Tyr Thr Phe Val Ile Val Pro Lys
65 70 75 80

Met Leu Val Asp Leu Leu Ser Gln Lys Lys Thr Ile Ser Phe Leu Gly
85 90 95

Cys Ala Ile Gln Met Phe Ser Phe Leu Phe Phe Gly Ser Ser His Ser
100 105 110

Phe Leu Leu Ala Ala Met Gly Tyr Asp Arg Tyr Met Ala Ile Cys Asn
115 120 125

Pro Leu Arg Tyr Ser Val Leu Met Gly His Gly Val Cys Met Gly Leu
130 135 140

Met Ala Ala Ala Cys Ala Cys Gly Phe Thr Val Ser Leu Val Thr Thr
145 150 155 160

Ser Leu Val Phe His Leu Pro Phe His Ser Ser Asn Gln Leu His His
165 170 175

Phe Phe Cys Asp Ile Ser Pro Val Leu Lys Leu Ala Ser Gln His Ser
180 185 190

Gly Phe Ser Gln Leu Val Ile Phe Met Leu Gly Val Phe Ala Leu Val
195 200 205

Ile Pro Leu Leu Leu Ile Leu Val Ser Tyr Ile Arg Ile Ile Ser Ala
210 215 220

Ile Leu Lys Ile Pro Ser Ser Val Gly Arg Tyr Lys Thr Phe Ser Thr
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Cys Ala Ser His Leu Ile Val Val Thr Val His Tyr Ser Cys Ala Ser
245 250 255

Phe Ile Tyr Leu Arg Pro Lys Thr Asn Tyr Thr Ser Ser Gln Asp Thr
260 265 270

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Ile Gly Gln Thr Phe Tyr Pro Leu Ser
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            20                  25                  30

att ccc ttg ctt ctc atc tac gga ttt atc cta act gga aac cta ata     144
Ile Pro Leu Leu Leu Ile Tyr Gly Phe Ile Leu Thr Gly Asn Leu Ile
        35                  40                  45

atg ttc att gtc atc cag gtg ggc atg gcc ctg cac acc cct ttg tat     192
Met Phe Ile Val Ile Gln Val Gly Met Ala Leu His Thr Pro Leu Tyr
    50                  55                  60

ttc ttt atc agt gtc ctc tcc ttc ctg gag atc tgc tat acc aca acc     240
Phe Phe Ile Ser Val Leu Ser Phe Leu Glu Ile Cys Tyr Thr Thr Thr
65                  70                  75                  80

acc atc ccc aag atg ctg tcc tgc cta atc agt gag cag aag agc att     288
Thr Ile Pro Lys Met Leu Ser Cys Leu Ile Ser Glu Gln Lys Ser Ile
                85                  90                  95

tcc gtg gct ggc tgc ctc ctg cag atg tac ttt ttc cac tca ctt ggt     336
Ser Val Ala Gly Cys Leu Leu Gln Met Tyr Phe Phe His Ser Leu Gly
            100                 105                 110

atc aca gaa agc tgt gtc ctg aca gca atg gcc att gac agg tac ata     384
Ile Thr Glu Ser Cys Val Leu Thr Ala Met Ala Ile Asp Arg Tyr Ile
        115                 120                 125

gct atc tgc aat cca ctc cgt tac cca acc atc atg att ccc aaa ctt     432
Ala Ile Cys Asn Pro Leu Arg Tyr Pro Thr Ile Met Ile Pro Lys Leu
    130                 135                 140

tgt atc cag ctg aca gtt gga tcc tgc ttt tgt ggc ttc ctc ctt gtg     480
Cys Ile Gln Leu Thr Val Gly Ser Cys Phe Cys Gly Phe Leu Leu Val
145                 150                 155                 160

ctt cct gag att gca tgg att tcc acc ttg cct ttc tgt ggc tcc aac     528
Leu Pro Glu Ile Ala Trp Ile Ser Thr Leu Pro Phe Cys Gly Ser Asn
                165                 170                 175

cag atc cac cag ata ttc tgt gat ttc aca cct gtg ctg agc ttg gcc     576
Gln Ile His Gln Ile Phe Cys Asp Phe Thr Pro Val Leu Ser Leu Ala
            180                 185                 190

tgc aca gat aca ttc cta gtg gtc att gtg gat gcc atc cat gca gcg     624
Cys Thr Asp Thr Phe Leu Val Val Ile Val Asp Ala Ile His Ala Ala
        195                 200                 205

gaa att gta gcc tcc ttc ctg gtc att gct cta tcc tac atc cgg att     672
Glu Ile Val Ala Ser Phe Leu Val Ile Ala Leu Ser Tyr Ile Arg Ile
    210                 215                 220

att ata gtg att ctg gga atg cac tca gct gaa ggt cat cac aag gcc     720
Ile Ile Val Ile Leu Gly Met His Ser Ala Glu Gly His His Lys Ala
225                 230                 235                 240

ttt tcc acc tgt gct gct cac ctt gct gtg ttc ttg cta ttt ttt ggc     768
Phe Ser Thr Cys Ala Ala His Leu Ala Val Phe Leu Leu Phe Phe Gly
                245                 250                 255

agt gtg gct gtc atg tat ttg aga ttc tca gcc acc tac tca gtg ttt     816
Ser Val Ala Val Met Tyr Leu Arg Phe Ser Ala Thr Tyr Ser Val Phe
            260                 265                 270

tgg gac aca gca att gct gtc act ttt gtt atc ctt gct ccc ttt ttc     864
Trp Asp Thr Ala Ile Ala Val Thr Phe Val Ile Leu Ala Pro Phe Phe
        275                 280                 285

aac ccc atc atc tat agc ctg aaa aac aag gac atg aaa gag gct att     912
Asn Pro Ile Ile Tyr Ser Leu Lys Asn Lys Asp Met Lys Glu Ala Ile
    290                 295                 300

gga agg ctt ttc cac tat cag aag agg gct ggt tgg gct ggg aaa tag     960
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35 40 45

Met Phe Ile Val Ile Gln Val Gly Met Ala Leu His Thr Pro Leu Tyr
50 55 60

Phe Phe Ile Ser Val Leu Ser Phe Leu Glu Ile Cys Tyr Thr Thr Thr
65 70 75 80

Thr Ile Pro Lys Met Leu Ser Cys Leu Ile Ser Glu Gln Lys Ser Ile
85 90 95

Ser Val Ala Gly Cys Leu Leu Gln Met Tyr Phe Phe His Ser Leu Gly
100 105 110

Ile Thr Glu Ser Cys Val Leu Thr Ala Met Ala Ile Asp Arg Tyr Ile
115 120 125

Ala Ile Cys Asn Pro Leu Arg Tyr Pro Thr Ile Met Ile Pro Lys Leu
130 135 140

Cys Ile Gln Leu Thr Val Gly Ser Cys Phe Cys Gly Phe Leu Leu Val
145 150 155 160

Leu Pro Glu Ile Ala Trp Ile Ser Thr Leu Pro Phe Cys Gly Ser Asn
165 170 175

Gln Ile His Gln Ile Phe Cys Asp Phe Thr Pro Val Leu Ser Leu Ala
180 185 190

Cys Thr Asp Thr Phe Leu Val Val Ile Val Asp Ala Ile His Ala Ala
195 200 205

Glu Ile Val Ala Ser Phe Leu Val Ile Ala Leu Ser Tyr Ile Arg Ile
210 215 220

Ile Ile Val Ile Leu Gly Met His Ser Ala Glu Gly His His Lys Ala
225 230 235 240

Phe Ser Thr Cys Ala Ala His Leu Ala Val Phe Leu Leu Phe Phe Gly
245 250 255

Ser Val Ala Val Met Tyr Leu Arg Phe Ser Ala Thr Tyr Ser Val Phe
260 265 270

Trp Asp Thr Ala Ile Ala Val Thr Phe Val Ile Leu Ala Pro Phe Phe
275 280 285

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cag atc ctt ctc ttc ttt atc ttc cta tta gtc tac ctg acc act ctg 96
Gln Ile Leu Leu Phe Phe Ile Phe Leu Leu Val Tyr Leu Thr Thr Leu
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atg gcc aac acc acc atc atg aca gtc att cac ctg gac agg gct ttg 144
Met Ala Asn Thr Thr Ile Met Thr Val Ile His Leu Asp Arg Ala Leu
35 40 45

cac act cct atg tac ttc ttc ctc ttt gtc ctt tca tgt tct gaa acc 192
His Thr Pro Met Tyr Phe Phe Leu Phe Val Leu Ser Cys Ser Glu Thr
50 55 60

tgc tac acc ttg gtc att gta ccc aaa atg ctt acc aac ctg cta tcc 240
Cys Tyr Thr Leu Val Ile Val Pro Lys Met Leu Thr Asn Leu Leu Ser
65 70 75 80

gca att cca act att tct ttc tct gga tgt gtg gtc cag ctc tat tta 288
Ala Ile Pro Thr Ile Ser Phe Ser Gly Cys Val Val Gln Leu Tyr Leu
85 90 95

ttt gtg ggc ttg gct tgt acc aac tgt ttt ctc att gct gtg atg ggc 336
Phe Val Gly Leu Ala Cys Thr Asn Cys Phe Leu Ile Ala Val Met Gly
100 105 110

tac gat cgc tat gtt gcc atc tgc aac ccc ctt aac tac aca ctc att 384
Tyr Asp Arg Tyr Val Ala Ile Cys Asn Pro Leu Asn Tyr Thr Leu Ile
115 120 125

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Asn Ile Leu Val Phe Ser Val Leu Leu Cys Ala Ser Asn Arg Ile Asn
145                 150                 155                 160

cac ttt ttc tgt gac att tcc cct gtc ata aaa ctg ggc tgc aca gac      528
His Phe Phe Cys Asp Ile Ser Pro Val Ile Lys Leu Gly Cys Thr Asp
                165                 170                 175

acc aac ctg aag gag atg gtc atc ttt ttc ctc agc att ctg gta ttg      576
Thr Asn Leu Lys Glu Met Val Ile Phe Phe Leu Ser Ile Leu Val Leu
            180                 185                 190

ctg gtt ccc ctt gtg ttg ata ttc atc tcc tac atc ttc ata gtt tcc      624
Leu Val Pro Leu Val Leu Ile Phe Ile Ser Tyr Ile Phe Ile Val Ser
        195                 200                 205

acc atc ctc aag atc tcc tca gtg gaa gga cag tgc aaa gcc ttc gcc      672
Thr Ile Leu Lys Ile Ser Ser Val Glu Gly Gln Cys Lys Ala Phe Ala
    210                 215                 220

acc tgt gct tcc cac ctc aca gtg gtc gtc gtc cac tat ggc tgt gct      720
Thr Cys Ala Ser His Leu Thr Val Val Val Val His Tyr Gly Cys Ala
225                 230                 235                 240

tcc ttt atc tac ttg agg ccc aca tcc ctg tac tct tca gat aag gac      768
Ser Phe Ile Tyr Leu Arg Pro Thr Ser Leu Tyr Ser Ser Asp Lys Asp
                245                 250                 255

cgg ctc gtg gca gtg act tat act gtg att act cca cta ctc aac ccc      816
Arg Leu Val Ala Val Thr Tyr Thr Val Ile Thr Pro Leu Leu Asn Pro
            260                 265                 270

ctt gtc tat aca ctg aga aat aaa gaa gta aag atg gct ctg aga aag      864
Leu Val Tyr Thr Leu Arg Asn Lys Glu Val Lys Met Ala Leu Arg Lys
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gtt ctg ggt aga tgc tta aat tcc aaa act gta tga                      900
Val Leu Gly Arg Cys Leu Asn Ser Lys Thr Val
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            20                  25                  30

Met Ala Asn Thr Thr Ile Met Thr Val Ile His Leu Asp Arg Ala Leu
        35                  40                  45

His Thr Pro Met Tyr Phe Phe Leu Phe Val Leu Ser Cys Ser Glu Thr
    50                  55                  60

Cys Tyr Thr Leu Val Ile Val Pro Lys Met Leu Thr Asn Leu Leu Ser
65                  70                  75                  80

Ala Ile Pro Thr Ile Ser Phe Ser Gly Cys Val Val Gln Leu Tyr Leu
                85                  90                  95

Phe Val Gly Leu Ala Cys Thr Asn Cys Phe Leu Ile Ala Val Met Gly
            100                 105                 110
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Tyr Asp Arg Tyr Val Ala Ile Cys Asn Pro Leu Asn Tyr Thr Leu Ile
115 120 125

Leu Val Leu Ala Ser Ser Phe Cys Gly Phe Leu Thr Ser Val Ile Val
130 135 140

Asn Ile Leu Val Phe Ser Val Leu Leu Cys Ala Ser Asn Arg Ile Asn
145 150 155 160

His Phe Phe Cys Asp Ile Ser Pro Val Ile Lys Leu Gly Cys Thr Asp
165 170 175

Thr Asn Leu Lys Glu Met Val Ile Phe Phe Leu Ser Ile Leu Val Leu
180 185 190

Leu Val Pro Leu Val Leu Ile Phe Ile Ser Tyr Ile Phe Ile Val Ser
195 200 205

Thr Ile Leu Lys Ile Ser Ser Val Glu Gly Gln Cys Lys Ala Phe Ala
210 215 220

Thr Cys Ala Ser His Leu Thr Val Val Val Val His Tyr Gly Cys Ala
225 230 235 240

Ser Phe Ile Tyr Leu Arg Pro Thr Ser Leu Tyr Ser Ser Asp Lys Asp
245 250 255

Arg Leu Val Ala Val Thr Tyr Thr Val Ile Thr Pro Leu Leu Asn Pro
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Val Leu Gly Arg Cys Leu Asn Ser Lys Thr Val
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atcactctgg tgtgttgaga tgaggctaca agtgaacaaa tgcaagtagg gagatctgtt 180

aggagtcaat tacagtaaga ggggagagat aaaagtgact tggaccgagg tggtcaaaca 240

tagtcagttc ctggatatat gagagaaaga tagaaacaag gatgactgca ggagtttagc 300

ttgtcagttg aaagattgca attgccatca tttgtgatgg ggaagactag gggtagagac 360

cccaggagtt cagtttgaga tggctcttcg actcccaaga ggagatgtga gtaggcagtg 420

aaatatatga gtctggagta gcagagaaaa atatcgcctg agatatggat ttagatgtct 480

tcaacacatt tatagtgttt aaagctctgg tattggatgg tatagagcag aggagttgag 540

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aaagtaacca aaagtatagt accccgagaa tcaagtcaag gaagtgtgtg aacaggctgg 720

ataaatcaat actgtcaaga aacagatagt ccaagtaagc tgaggaatga gaaatgacca 780

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caatgcgtat agccgactct tggaagagtt ttcttttagg gacatagaaa gaaatagagc 960

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caaattaaaa tgagaaatta gaaaataata ttcaaattat atatatttgg tccagtacgg   1620

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gagagaaggg agggcaatag taatttgagg gttgccttct tgttagaacc ctatagttca   1980

actttctttc ctatccttcc acacttcaca tctagggaca tgaatggtga gca atg       2036
                                                            Met
                                                             1

gac aca ggg aac tgg agc cag gta gca gaa ttc atc atc ttg ggc ttc      2084
Asp Thr Gly Asn Trp Ser Gln Val Ala Glu Phe Ile Ile Leu Gly Phe
            5                  10                  15

ccc cat ctc cag ggt gtc cag att tat ctc ttc ctc ttg ttg ctt ctc      2132
Pro His Leu Gln Gly Val Gln Ile Tyr Leu Phe Leu Leu Leu Leu Leu
        20                  25                  30

att tac ctc atg act gtg ttg gga aac ctg ctg ata ttc ctg gtg gtc      2180
Ile Tyr Leu Met Thr Val Leu Gly Asn Leu Leu Ile Phe Leu Val Val
    35                  40                  45

tgc ctg gac tcc cgg ctt cac aca ccc atg tac cac ttt gtc agc att      2228
Cys Leu Asp Ser Arg Leu His Thr Pro Met Tyr His Phe Val Ser Ile
50                  55                  60                  65

ctc tcc ttc tca gag ctt ggc tat aca gct gcc acc atc cct aag atg      2276
Leu Ser Phe Ser Glu Leu Gly Tyr Thr Ala Ala Thr Ile Pro Lys Met
                70                  75                  80

ctg gca aac ttg ctc agt gag aaa aag acc att tca ttc tct ggg tgt      2324
Leu Ala Asn Leu Leu Ser Glu Lys Lys Thr Ile Ser Phe Ser Gly Cys
            85                  90                  95

ctc ctg cag atc tat ttc ttt cac tcc ctt gga gcg act gag tgc tat      2372
Leu Leu Gln Ile Tyr Phe Phe His Ser Leu Gly Ala Thr Glu Cys Tyr
        100                 105                 110

ctc ctg aca gct atg gcc tac gat agg tat tta gcc atc tgc cgg ccc      2420
Leu Leu Thr Ala Met Ala Tyr Asp Arg Tyr Leu Ala Ile Cys Arg Pro
    115                 120                 125

ctc cac tac cca acc ctc atg acc cca aca ctt tgt gca gag att gcc      2468
Leu His Tyr Pro Thr Leu Met Thr Pro Thr Leu Cys Ala Glu Ile Ala
130                 135                 140                 145

att ggc tgt tgg ttg gga ggc ttg gct ggg cca gta gtt gaa att tcc      2516
Ile Gly Cys Trp Leu Gly Gly Leu Ala Gly Pro Val Val Glu Ile Ser
                150                 155                 160

ttg att tca cgc ctc cca ttc tgt ggc ccc aat cgc att cag cac gtc      2564
Leu Ile Ser Arg Leu Pro Phe Cys Gly Pro Asn Arg Ile Gln His Val
            165                 170                 175

ttt tgt gac ttc cct cct gtg ctg agt ttg gct tgc act gat acg tct      2612
Phe Cys Asp Phe Pro Pro Val Leu Ser Leu Ala Cys Thr Asp Thr Ser
        180                 185                 190

ata aat gtc cta gta gat ttt gtt ata aat tcc tgc aag atc cta gcc      2660
Ile Asn Val Leu Val Asp Phe Val Ile Asn Ser Cys Lys Ile Leu Ala
    195                 200                 205

acc ttc ctg ctg atc ctc tgc tcc tat gtg cag atc atc tgc aca gtg      2708
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                230                 235                 240

gcc tcc cac ttc act gtg gtt ctc atc ttc tat ggg agc atc ctt tcc     2804
Ala Ser His Phe Thr Val Val Leu Ile Phe Tyr Gly Ser Ile Leu Ser
            245                 250                 255

atg tat gtg cag ctg aag aag agc tac tca ctg gac tat gac cag gcc     2852
Met Tyr Val Gln Leu Lys Lys Ser Tyr Ser Leu Asp Tyr Asp Gln Ala
        260                 265                 270

ctg gca gtg gtc tac tca gtg ctc aca ccc ttc ctc aac ccc ttc atc     2900
Leu Ala Val Val Tyr Ser Val Leu Thr Pro Phe Leu Asn Pro Phe Ile
    275                 280                 285

tac agc ttg cgc aac aag gag atc aag gag gct gtg agg agg cag cta     2948
Tyr Ser Leu Arg Asn Lys Glu Ile Lys Glu Ala Val Arg Arg Gln Leu
290                 295                 300                 305

aag aga att ggg ata ttg gca tga gttggggctg agagtaggcc aaggccgggc    3002
Lys Arg Ile Gly Ile Leu Ala
                310

ctgaggatat ggtggcccca gggatcaaca gtggccagag acgagaaact aaaaattcag    3062

tgcttttcta tgtggggtgg tggagctgca gcaagtgctg actgacttcc agtgttatag    3122

cgaccttcat actgtctgct ggagccacat ttggcttgag accagagact agggaaagta    3182

cacatccctt caacatgatg tagtgcagtg attttcaaaa ctcagatgtt tatgtatcac    3242

acttaggttt tttttaaaat ctgtgtctta cctattatac gtttataggc atttttcaaa    3302

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gtctgacatg taggtgatag taaataaata aggacttgtt tttatttatt ttattctgcg    3662

aagacttcac atcattactc tgggtcttag aacaatatct agtaaaacat aaataaacaa    3722

aaatactttc caagtatttt ctccaaagga aaggagcaaa ccagccagaa ggaatacttg    3782

tatagtatac aagtatacta tacttgaaaa gtatagtttg tcacagttct gttctgacaa    3842

gtttcatgta cctgtcttag tggtcctaat atctatggcc agtataatgt atgaaagtat    3902

aggagttgag tcagtggaaa gaaataggat tacttttac atcgaaccat ttctttattg    3962

aattgtaagc taattatttc ctgaaacgtg tgaaaaataa ttctaaaatg tagcatatga    4022

gagatctggg gattcaatta atagctaata ttatgtattc tttatgtatc cttccatgaa    4082

tggaggatca aatatttaact acaagaaatc tttgaattct atagaacttc ctaagaagat    4142

tacaaaatat ttttaatacc acacttttaa aggtattcat ccatccatgc attcaaatta    4202

acacgtttat ttagctctta ctatatatca gatgcagtgt caactctaca aaagcaatga    4262

acaagacata tatatgtcca ggtcctacct ttagggtgtt ttaaaagagt tgagaatata    4322

aatattaaaa ttataattaa tttataatta gttataatta attataattg tgggaagtag    4382

tattaagata aacatgcatt ctccttttt ttcacttgtc tttgaagttt attgagaatt    4442

ttaagcagat aaatgttttt acattaaata atcaccagga attcaaaata ttatactcta    4502

tcaaatggga acttgaattg ttctatttat atatgtagca ttctatttat aaatatattt    4562

catttagtgt ttcatctaga ataaaaatga caagaaataa aattattaaa aacaagttgt    4622
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ctatgctagg taaatttgcc cctattattt tctttttttat tttattttat tttatttcat 4742

tattatttta tttagggtac atgtgcacaa cgtgcaagtt ttttacatat gtatacatgt 4802

gccatgttgg tgtgctgcac ccattaactc atcatttagc attaggagta tctcctaatg 4862

ctatccctcc cccatccccc aaccccacaa cagtccccag tgtgtgatgt tccccttctc 4922

aatatcatac tgaatgggca aaaactggaa gcattccctt tgaaaacggg cacaagacag 4982

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20 25 30

Leu Ile Tyr Leu Met Thr Val Leu Gly Asn Leu Leu Ile Phe Leu Val
35 40 45

Val Cys Leu Asp Ser Arg Leu His Thr Pro Met Tyr His Phe Val Ser
50 55 60

Ile Leu Ser Phe Ser Glu Leu Gly Tyr Thr Ala Ala Thr Ile Pro Lys
65 70 75 80

Met Leu Ala Asn Leu Leu Ser Glu Lys Lys Thr Ile Ser Phe Ser Gly
85 90 95

Cys Leu Leu Gln Ile Tyr Phe Phe His Ser Leu Gly Ala Thr Glu Cys
100 105 110

Tyr Leu Leu Thr Ala Met Ala Tyr Asp Arg Tyr Leu Ala Ile Cys Arg
115 120 125

Pro Leu His Tyr Pro Thr Leu Met Thr Pro Thr Leu Cys Ala Glu Ile
130 135 140

Ala Ile Gly Cys Trp Leu Gly Gly Leu Ala Gly Pro Val Val Glu Ile
145 150 155 160

Ser Leu Ile Ser Arg Leu Pro Phe Cys Gly Pro Asn Arg Ile Gln His
165 170 175

Val Phe Cys Asp Phe Pro Pro Val Leu Ser Leu Ala Cys Thr Asp Thr
180 185 190

Ser Ile Asn Val Leu Val Asp Phe Val Ile Asn Ser Cys Lys Ile Leu
195 200 205

Ala Thr Phe Leu Leu Ile Leu Cys Ser Tyr Val Gln Ile Ile Cys Thr
210 215 220

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Val Leu Arg Ile Pro Ser Ala Ala Gly Lys Arg Lys Ala Ile Ser Thr
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Cys Ala Ser His Phe Thr Val Val Leu Ile Phe Tyr Gly Ser Ile Leu
245 250 255

Ser Met Tyr Val Gln Leu Lys Lys Ser Tyr Ser Leu Asp Tyr Asp Gln
260 265 270

Ala Leu Ala Val Val Tyr Ser Val Leu Thr Pro Phe Leu Asn Pro Phe
275 280 285

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290 295 300

Leu Lys Arg Ile Gly Ile Leu Ala
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      1               5                  10                  15

ggt ttc acc acc act ggg acc cta caa cct ctt gcc ttc ttg ggg acc      98
Gly Phe Thr Thr Thr Gly Thr Leu Gln Pro Leu Ala Phe Leu Gly Thr
                 20                  25                  30

cta tgc atc tat ctc ctc aca ctt gca ggg aac att ctc atc att gtc     146
Leu Cys Ile Tyr Leu Leu Thr Leu Ala Gly Asn Ile Leu Ile Ile Val
             35                  40                  45

ctg agg tgt ggt atg tca gca cca cag tgc cca tgc tgc tgc aca cct     194
Leu Arg Cys Gly Met Ser Ala Pro Gln Cys Pro Cys Cys Cys Thr Pro
         50                  55                  60

tgc tcc aag ggt gtt cac ccg tct cat cag ctg tat gct tta ttc agc     242
Cys Ser Lys Gly Val His Pro Ser His Gln Leu Tyr Ala Leu Phe Ser
     65                  70                  75

tat gtc ttt cat tcc tta ggg atg act gag tgc tac ctg ctg ggt gtc     290
Tyr Val Phe His Ser Leu Gly Met Thr Glu Cys Tyr Leu Leu Gly Val
80                  85                  90                  95

atg gca ctg gat agc tac ctt atc atc tgc cac cca ctc cac tac cac     338
Met Ala Leu Asp Ser Tyr Leu Ile Ile Cys His Pro Leu His Tyr His
                100                 105                 110

gca ctc atg agc aga cag gta cag tta cga cta gct ggg gcc agt tgg     386
Ala Leu Met Ser Arg Gln Val Gln Leu Arg Leu Ala Gly Ala Ser Trp
            115                 120                 125

gtg gct ggc ttc tca gct gca ctt gtg cca gcc acc ctc act gcc act     434
Val Ala Gly Phe Ser Ala Ala Leu Val Pro Ala Thr Leu Thr Ala Thr
        130                 135                 140

ctg ccc ttc tgc ttg aaa gag gtg gcc cat tac ttt tgt gac ttg gca     482
Leu Pro Phe Cys Leu Lys Glu Val Ala His Tyr Phe Cys Asp Leu Ala
    145                 150                 155

cca cta atg cgg ttg gca tgt gtg gac aca agc tgg cat gct agg gcc     530
Pro Leu Met Arg Leu Ala Cys Val Asp Thr Ser Trp His Ala Arg Ala
160                 165                 170                 175

cat ggc aca gtg att ggt gtg gcc act ggt tgc aac ttt gtg ctc att     578
His Gly Thr Val Ile Gly Val Ala Thr Gly Cys Asn Phe Val Leu Ile
                180                 185                 190

ttg gga ctc tat gga ggt atc ctg aat gct gtg ctg aag cta ccc tca     626
Leu Gly Leu Tyr Gly Gly Ile Leu Asn Ala Val Leu Lys Leu Pro Ser
            195                 200                 205

gct gcc agt agt gcc aag gcc ttc tct acc tgt tcc tcc cac gta act     674
Ala Ala Ser Ser Ala Lys Ala Phe Ser Thr Cys Ser Ser His Val Thr
        210                 215                 220

gtg gtg gca cta ttc tat gct tct gcc ttc aca gta tat gtg ggc tca     722
Val Val Ala Leu Phe Tyr Ala Ser Ala Phe Thr Val Tyr Val Gly Ser
    225                 230                 235

cct ggg agt cga cct gag agc aca gac aag ctt gtt gcc ttg gtt tat     770
Pro Gly Ser Arg Pro Glu Ser Thr Asp Lys Leu Val Ala Leu Val Tyr
240                 245                 250                 255

gcc ctt att acc cct ttc ctc aat cct atc atc tat agc ctt cgc aac     818
Ala Leu Ile Thr Pro Phe Leu Asn Pro Ile Ile Tyr Ser Leu Arg Asn
                260                 265                 270

aag gag ctc ctc tat tgc ttc ctc tgc tga                            848
Lys Glu Leu Leu Tyr Cys Phe Leu Cys
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<213> Homo sapiens

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Cys Ile Tyr Leu Leu Thr Leu Ala Gly Asn Ile Leu Ile Ile Val Leu
35 40 45

Arg Cys Gly Met Ser Ala Pro Gln Cys Pro Cys Cys Cys Thr Pro Cys
50 55 60

Ser Lys Gly Val His Pro Ser His Gln Leu Tyr Ala Leu Phe Ser Tyr
65 70 75 80

Val Phe His Ser Leu Gly Met Thr Glu Cys Tyr Leu Leu Gly Val Met
85 90 95

Ala Leu Asp Ser Tyr Leu Ile Ile Cys His Pro Leu His Tyr His Ala
100 105 110

Leu Met Ser Arg Gln Val Gln Leu Arg Leu Ala Gly Ala Ser Trp Val
115 120 125

Ala Gly Phe Ser Ala Ala Leu Val Pro Ala Thr Leu Thr Ala Thr Leu
130 135 140

Pro Phe Cys Leu Lys Glu Val Ala His Tyr Phe Cys Asp Leu Ala Pro
145 150 155 160

Leu Met Arg Leu Ala Cys Val Asp Thr Ser Trp His Ala Arg Ala His
165 170 175

Gly Thr Val Ile Gly Val Ala Thr Gly Cys Asn Phe Val Leu Ile Leu
180 185 190

Gly Leu Tyr Gly Gly Ile Leu Asn Ala Val Leu Lys Leu Pro Ser Ala
195 200 205

Ala Ser Ser Ala Lys Ala Phe Ser Thr Cys Ser Ser His Val Thr Val
210 215 220

Val Ala Leu Phe Tyr Ala Ser Ala Phe Thr Val Tyr Val Gly Ser Pro
225 230 235 240

Gly Ser Arg Pro Glu Ser Thr Asp Lys Leu Val Ala Leu Val Tyr Ala
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Leu Ile Thr Pro Phe Leu Asn Pro Ile Ile Tyr Ser Leu Arg Asn Lys
260 265 270

Glu Leu Leu Tyr Cys Phe Leu Cys
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cag ctg gcc ctc ttt gta gtt ttt ctt ttt ctg tat cta gtc att ctt 96
Gln Leu Ala Leu Phe Val Val Phe Leu Phe Leu Tyr Leu Val Ile Leu
20 25 30

agt ggc aat gtc acc att atc agt gtc atc cac ctg gat aaa agc ctc 144
Ser Gly Asn Val Thr Ile Ile Ser Val Ile His Leu Asp Lys Ser Leu
35 40 45

cac aca cca atg tac ttc ttc ctt ggc att ctc tca aca tct gag acc 192
His Thr Pro Met Tyr Phe Phe Leu Gly Ile Leu Ser Thr Ser Glu Thr
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Phe Tyr Thr Phe Val Ile Leu Pro Lys Met Leu Ile Asn Leu Leu Ser
65 70 75 80

gtg gcc agg aca atc tcc ttc aac tgt tgt gct ctt caa atg ttc ttc 288
Val Ala Arg Thr Ile Ser Phe Asn Cys Cys Ala Leu Gln Met Phe Phe
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atg agc tgg cag gtg tgt gga aaa ctg gca gct gcc tgt gca att ggt      432
Met Ser Trp Gln Val Cys Gly Lys Leu Ala Ala Ala Cys Ala Ile Gly
    130                 135                 140

ggc ttc ttg gcc tct ctt aca gta gta aat tta gtt ttc agc ctc cct      480
Gly Phe Leu Ala Ser Leu Thr Val Val Asn Leu Val Phe Ser Leu Pro
145                 150                 155                 160

ttt tgt agc gcc aac aaa gtc aat cat tac ttc tgt gac atc tca gca      528
Phe Cys Ser Ala Asn Lys Val Asn His Tyr Phe Cys Asp Ile Ser Ala
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Val Ile Leu Leu Ala Cys Thr Asn Thr Asp Val Asn Glu Phe Val Ile
            180                 185                 190

ttc att tgt gga gtt ctt gta ctt gtg gtt ccc ttt ctg ttt atc tgt      624
Phe Ile Cys Gly Val Leu Val Leu Val Val Pro Phe Leu Phe Ile Cys
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gtt tct tat ctc tgc att ctg agg act atc ctg aag att ccc tca gct      672
Val Ser Tyr Leu Cys Ile Leu Arg Thr Ile Leu Lys Ile Pro Ser Ala
    210                 215                 220

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Glu Gly Arg Arg Lys Ala Phe Ser Thr Cys Ala Ser His Leu Ser Val
225                 230                 235                 240

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Val Ile Val His Tyr Gly Cys Ala Ser Phe Ile Tyr Leu Arg Pro Thr
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Ala Asn Tyr Val Ser Asn Lys Asp Arg Leu Val Thr Val Thr Tyr Thr
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Ile Val Thr Pro Leu Leu Asn Pro Met Val Tyr Ser Leu Arg Asn Lys
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gat gtc caa ctt gct atc aga aaa gtg ttg ggc aag aaa ggt att ctt      912
Asp Val Gln Leu Ala Ile Arg Lys Val Leu Gly Lys Lys Gly Ile Leu
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tct atc tct gaa atc ttc tac aca act gtt att ctg ccc aag atg ctt      960
Ser Ile Ser Glu Ile Phe Tyr Thr Thr Val Ile Leu Pro Lys Met Leu
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atc aac tta ttc tct gta ttc agg aca ctc tcc ttt gtg agt tgt gcc     1008
Ile Asn Leu Phe Ser Val Phe Arg Thr Leu Ser Phe Val Ser Cys Ala
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acc caa atg ttc ttc ttc ctc ggt ttt gct gtc act aac tgt ctg ctt     1056
Thr Gln Met Phe Phe Phe Leu Gly Phe Ala Val Thr Asn Cys Leu Leu
            340                 345                 350

ctg gga gtg atg ggt tat gat cgt tat gct gcc atc tgt cag cct ttg     1104
Leu Gly Val Met Gly Tyr Asp Arg Tyr Ala Ala Ile Cys Gln Pro Leu
        355                 360                 365

caa tac gct gtt ctc atg agc tgg aga gta tgt gga caa ctg ata gca     1152
Gln Tyr Ala Val Leu Met Ser Trp Arg Val Cys Gly Gln Leu Ile Ala
    370                 375                 380

act tgt att att agt ggc ttc cta ata tct ctg gtg gga aca act ttt     1200
Thr Cys Ile Ile Ser Gly Phe Leu Ile Ser Leu Val Gly Thr Thr Phe
385                 390                 395                 400

gtc ttt agc ctc cct ttc tgt ggc tcc aac aag gtc aac cac tac ttt     1248
Val Phe Ser Leu Pro Phe Cys Gly Ser Asn Lys Val Asn His Tyr Phe
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Ser Glu Leu Val Ile Phe Ile Phe Gly Val Leu Val Leu Val Val Pro
        435                 440                 445

ttg ata ttt atc tgc att tcc tat ggc ttc att gtc cgc acc atc ctg     1392
Leu Ile Phe Ile Cys Ile Ser Tyr Gly Phe Ile Val Arg Thr Ile Leu
    450                 455                 460

aag atc cca tca gct gaa ggc aaa caa aaa gcc ttc tcc acc tgt gct     1440
Lys Ile Pro Ser Ala Glu Gly Lys Gln Lys Ala Phe Ser Thr Cys Ala
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tcc cat ctc att gta gtc att gtc cat tat ggt tga                     1476
Ser His Leu Ile Val Val Ile Val His Tyr Gly
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            20                  25                  30


Ser Gly Asn Val Thr Ile Ile Ser Val Ile His Leu Asp Lys Ser Leu
        35                  40                  45


His Thr Pro Met Tyr Phe Phe Leu Gly Ile Leu Ser Thr Ser Glu Thr
    50                  55                  60


Phe Tyr Thr Phe Val Ile Leu Pro Lys Met Leu Ile Asn Leu Leu Ser
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Val Ala Arg Thr Ile Ser Phe Asn Cys Cys Ala Leu Gln Met Phe Phe
                85                  90                  95


Phe Leu Gly Phe Ala Ile Thr Asn Cys Leu Leu Leu Gly Val Met Gly
            100                 105                 110


Tyr Asp Arg Tyr Ala Ala Ile Cys His Pro Leu His Tyr Pro Thr Leu
        115                 120                 125


Met Ser Trp Gln Val Cys Gly Lys Leu Ala Ala Ala Cys Ala Ile Gly
    130                 135                 140


Gly Phe Leu Ala Ser Leu Thr Val Val Asn Leu Val Phe Ser Leu Pro
145                 150                 155                 160


Phe Cys Ser Ala Asn Lys Val Asn His Tyr Phe Cys Asp Ile Ser Ala
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Val Ile Leu Leu Ala Cys Thr Asn Thr Asp Val Asn Glu Phe Val Ile
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Phe Ile Cys Gly Val Leu Val Leu Val Val Pro Phe Leu Phe Ile Cys
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Val Ile Val His Tyr Gly Cys Ala Ser Phe Ile Tyr Leu Arg Pro Thr
245 250 255

Ala Asn Tyr Val Ser Asn Lys Asp Arg Leu Val Thr Val Thr Tyr Thr
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Ile Val Thr Pro Leu Leu Asn Pro Met Val Tyr Ser Leu Arg Asn Lys
275 280 285

Asp Val Gln Leu Ala Ile Arg Lys Val Leu Gly Lys Lys Gly Ile Leu
290 295 300

Ser Ile Ser Glu Ile Phe Tyr Thr Thr Val Ile Leu Pro Lys Met Leu
305 310 315 320

Ile Asn Leu Phe Ser Val Phe Arg Thr Leu Ser Phe Val Ser Cys Ala
325 330 335

Thr Gln Met Phe Phe Phe Leu Gly Phe Ala Val Thr Asn Cys Leu Leu
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Leu Gly Val Met Gly Tyr Asp Arg Tyr Ala Ala Ile Cys Gln Pro Leu
355 360 365

Gln Tyr Ala Val Leu Met Ser Trp Arg Val Cys Gly Gln Leu Ile Ala
370 375 380

Thr Cys Ile Ile Ser Gly Phe Leu Ile Ser Leu Val Gly Thr Thr Phe
385 390 395 400

Val Phe Ser Leu Pro Phe Cys Gly Ser Asn Lys Val Asn His Tyr Phe
405 410 415

Cys Asp Ile Ser Pro Val Ile Arg Leu Ala Cys Ala Asp Ser Tyr Ile
420 425 430

Ser Glu Leu Val Ile Phe Ile Phe Gly Val Leu Val Leu Val Val Pro
435 440 445

Leu Ile Phe Ile Cys Ile Ser Tyr Gly Phe Ile Val Arg Thr Ile Leu
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Ser His Leu Ile Val Val Ile Val His Tyr Gly
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Pro Val Leu Thr Ser Trp Gln Ile Cys Ser Phe Leu Asp Phe Gln Leu
20 25 30

ctt ttc tgt ggc cca aac aag atc aac cac tac ttc tgt gac atc tca 144
Leu Phe Cys Gly Pro Asn Lys Ile Asn His Tyr Phe Cys Asp Ile Ser
35 40 45

ctg ctt att cag ctt gcc tgt act gat acc tac atc agg gag cta gtc 192
Leu Leu Ile Gln Leu Ala Cys Thr Asp Thr Tyr Ile Arg Glu Leu Val
50 55 60

atc ttc att ggt gga att cta gca ctt acg gtt cct ctg att tta ttt 240
Ile Phe Ile Gly Gly Ile Leu Ala Leu Thr Val Pro Leu Ile Leu Phe
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gca tct cct atg gct tca ttg ttc aca cca tcc tga 276

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35 40 45

Leu Leu Ile Gln Leu Ala Cys Thr Asp Thr Tyr Ile Arg Glu Leu Val
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    20                  25                  30

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Ile Tyr Asn Val Thr Val Leu Gly Asn Ile Gly Leu Ile Val Ile Ile
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aaa atc aac ccc aaa ctg cat acc ccc atg tac ttt ttc ctc agc caa      2408
Lys Ile Asn Pro Lys Leu His Thr Pro Met Tyr Phe Phe Leu Ser Gln
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ctc tcc ttt gtg gat ttc tgc tat tcc tcc atc att gct ccc aag atg      2456
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Val Val Gln Phe Phe Phe Phe Cys Thr Phe Val Val Thr Glu Ser Phe
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gtg gga tcc tat gcc tgg gga gtc tca tgt tcc ttg gaa ctg acg tgc      2696
Val Gly Ser Tyr Ala Trp Gly Val Ser Cys Ser Leu Glu Leu Thr Cys
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Phe Cys Glu Phe Ser Ser Leu Leu Ser Leu Ser Cys Ser Asp Thr Tyr
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    260                 265                 270

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Ala Ser Val Phe Tyr Thr Val Val Ile Pro Met Leu Asn Pro Leu Ile
275                 280                 285                 290

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Asp Thr Lys Val Phe Ser Tyr
            310

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Ile Ile Lys Ile Asn Pro Lys Leu His Thr Pro Met Tyr Phe Phe Leu
50 55 60

Ser Gln Leu Ser Phe Val Asp Phe Cys Tyr Ser Ser Ile Ile Ala Pro
65 70 75 80

Lys Met Leu Val Asn Leu Val Val Lys Asp Arg Thr Ile Ser Phe Leu
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Gly Cys Val Val Gln Phe Phe Phe Phe Cys Thr Phe Val Val Thr Glu
100 105 110

Ser Phe Leu Leu Ala Val Met Ala Tyr Asp Arg Phe Val Ala Ile Cys
115 120 125

Asn Pro Leu Leu Tyr Thr Val Asn Met Ser Gln Lys Leu Cys Val Leu
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Leu Val Val Gly Ser Tyr Ala Trp Gly Val Ser Cys Ser Leu Glu Leu
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Thr Cys Ser Ala Leu Lys Leu Cys Phe His Gly Phe Asn Thr Ile Asn
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His Phe Phe Cys Glu Phe Ser Ser Leu Leu Ser Leu Ser Cys Ser Asp
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Thr Tyr Ile Asn Gln Trp Leu Leu Phe Phe Leu Ala Thr Phe Asn Glu
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Ile Ser Thr Leu Leu Ile Val Leu Thr Ser Tyr Ala Phe Ile Val Val
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Pro Thr Ala Phe Leu Leu Val Gly Ile Pro Gly Leu Glu His Leu His
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Ile Trp Ile Ser Ile Pro Phe Cys Leu Ala Tyr Thr Leu Ala Leu Leu
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gga aac tgc act ctc ctt ctc atc atc cag gct gat gca gcc ctc cat 1995
Gly Asn Cys Thr Leu Leu Leu Ile Ile Gln Ala Asp Ala Ala Leu His
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gaa ccc atg tac ctc ttt ctg gcc atg ttg gca gcc atc gac ctg gtc 2043
Glu Pro Met Tyr Leu Phe Leu Ala Met Leu Ala Ala Ile Asp Leu Val
60 65 70

ctt tcc tcc tca gca ctg ccc aaa atg ctt gcc ata ttc tgg ttc agg 2091
Leu Ser Ser Ser Ala Leu Pro Lys Met Leu Ala Ile Phe Trp Phe Arg
75 80 85 90

gat cgg gag ata aac ttc ttt gcc tgt ctg gcc cag atg ttc ttc ctt 2139
Asp Arg Glu Ile Asn Phe Phe Ala Cys Leu Ala Gln Met Phe Phe Leu
95 100 105

cac tcc ttc tcc atc atg gag tca gca gtg ctg ctg gcc atg gcc ttt 2187
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act ggg tcc ctc atc acc aag att ggc atg gct gct gtg gcc cgg gct      2283
Thr Gly Ser Leu Ile Thr Lys Ile Gly Met Ala Ala Val Ala Arg Ala
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gtg aca cta atg act cca ctc ccc ttc ctg ctg aga tgt ttc cac tac      2331
Val Thr Leu Met Thr Pro Leu Pro Phe Leu Leu Arg Cys Phe His Tyr
155                 160                 165                 170

tgc cga ggc cca gtg atc gct cac tgc tac tgt gaa cac atg gct gtg      2379
Cys Arg Gly Pro Val Ile Ala His Cys Tyr Cys Glu His Met Ala Val
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Val Arg Leu Ala Cys Gly Asp Thr Ser Phe Asn Asn Ile Tyr Gly Ile
            190                 195                 200

gct gtg gcc atg ttt att gtg gtg ttg gac ctg ctc ctt gtt atc ctg      2475
Ala Val Ala Met Phe Ile Val Val Leu Asp Leu Leu Leu Val Ile Leu
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tct tat atc ttt att ctt cag gca gtt cta ctg ctt gcc tct cag gag      2523
Ser Tyr Ile Phe Ile Leu Gln Ala Val Leu Leu Leu Ala Ser Gln Glu
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gcc cac tac aag gca ttt ggg aca tgt gtc tct cat ata ggt gcc atc      2571
Ala His Tyr Lys Ala Phe Gly Thr Cys Val Ser His Ile Gly Ala Ile
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tta gcc ttc tac aca act gtg gtc atc tct tca gtc atg cac cgt gta      2619
Leu Ala Phe Tyr Thr Thr Val Val Ile Ser Ser Val Met His Arg Val
                255                 260                 265

gcc cgc cat gct gcc cct cat gtc cac atc ctc ctt gcc aat ttc tat      2667
Ala Arg His Ala Ala Pro His Val His Ile Leu Leu Ala Asn Phe Tyr
            270                 275                 280

ctg ctc ttc cca ccc atg gtc aat ccc ata atc tat ggt gtc aag acc      2715
Leu Leu Phe Pro Pro Met Val Asn Pro Ile Ile Tyr Gly Val Lys Thr
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aag caa atc cgt gag agc atc ttg gga gta ttc cca aga aag gat atg      2763
Lys Gln Ile Arg Glu Ser Ile Leu Gly Val Phe Pro Arg Lys Asp Met
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gatagattct gttctctgaa atttccatcc caaggcccag cataataaaa gaagagcaag   3656

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Phe Cys Leu Ala Tyr Thr Leu Ala Leu Leu Gly Asn Cys Thr Leu Leu
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Leu Ala Met Leu Ala Ala Ile Asp Leu Val Leu Ser Ser Ser Ala Leu
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Pro Lys Met Leu Ala Ile Phe Trp Phe Arg Asp Arg Glu Ile Asn Phe
85 90 95

Phe Ala Cys Leu Ala Gln Met Phe Phe Leu His Ser Phe Ser Ile Met
100 105 110

Glu Ser Ala Val Leu Leu Ala Met Ala Phe Asp Arg Tyr Val Ala Ile
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195 200 205

Val Val Leu Asp Leu Leu Leu Val Ile Leu Ser Tyr Ile Phe Ile Leu
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Gln Ala Val Leu Leu Leu Ala Ser Gln Glu Ala His Tyr Lys Ala Phe
225 230 235 240

Gly Thr Cys Val Ser His Ile Gly Ala Ile Leu Ala Phe Tyr Thr Thr
245 250 255

Val Val Ile Ser Ser Val Met His Arg Val Ala Arg His Ala Ala Pro
260 265 270

His Val His Ile Leu Leu Ala Asn Phe Tyr Leu Leu Phe Pro Pro Met
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acagtg atg gag tgg acg gcg gca cgg gcc cga ccc ttg gtg atg acc 768
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ttg aac tct ctg ggc ttc agc ttc ggc cat ggc ctg aca gct gca gtg 816
Leu Asn Ser Leu Gly Phe Ser Phe Gly His Gly Leu Thr Ala Ala Val
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gcc tac ggt gtg cgg gac tgg aca ctg ctg cag ctg gtg gtc tcg gtc 864
Ala Tyr Gly Val Arg Asp Trp Thr Leu Leu Gln Leu Val Val Ser Val
35 40 45

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Pro Phe Phe Leu Cys Phe Leu Tyr Ser Trp Trp Leu Ala Glu Ser Ala
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acc cct gag gtc ttg ctt tca gcc atg cgg gag gag ctg agc atg ggc      1056
Thr Pro Glu Val Leu Leu Ser Ala Met Arg Glu Glu Leu Ser Met Gly
95                  100                 105                 110

cag cct cct gcc agc ctg ggc acc ctg ctc cgc atg ccc gga ctg cgc      1104
Gln Pro Pro Ala Ser Leu Gly Thr Leu Leu Arg Met Pro Gly Leu Arg
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ttc cgg acc tgt atc tcc acg ttg tgc tgg ttc gcc ttt ggc ttc acc      1152
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ttc ttc ggc ctg gcc ctg gac ctg cag gcc ctg ggc agc aac atc ttc      1200
Phe Phe Gly Leu Ala Leu Asp Leu Gln Ala Leu Gly Ser Asn Ile Phe
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ctg ctc caa atg ttc att ggt gtc gtg gac atc cca gcc aag atg ggc      1248
Leu Leu Gln Met Phe Ile Gly Val Val Asp Ile Pro Ala Lys Met Gly
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gcc ctg ctg ctg ctg agc cac ctg ggc cgc cgc ccc acg ctg gcc gca      1296
Ala Leu Leu Leu Leu Ser His Leu Gly Arg Arg Pro Thr Leu Ala Ala
175                 180                 185                 190

tcc ctg ttg ctg gca ggg ctc tgc att ctg gcc aac acg ctg gtg ccc      1344
Ser Leu Leu Leu Ala Gly Leu Cys Ile Leu Ala Asn Thr Leu Val Pro
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cac gaa atg ggg gct ctg cgc tca gcc ttg gcc gtg ctg ggg ctg ggc      1392
His Glu Met Gly Ala Leu Arg Ser Ala Leu Ala Val Leu Gly Leu Gly
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ggg gtg ggg gct gcc ttc acc tgc atc acc atc tac agc agc gag ctc      1440
Gly Val Gly Ala Ala Phe Thr Cys Ile Thr Ile Tyr Ser Ser Glu Leu
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ttc ccc act gtg ctc agg atg acg gca gtg ggc ttg ggc cag atg gca      1488
Phe Pro Thr Val Leu Arg Met Thr Ala Val Gly Leu Gly Gln Met Ala
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gcc cgt gga gga gcc atc ctg ggg cct ctg gtc cgg ctg ctg ggt gtc      1536
Ala Arg Gly Gly Ala Ile Leu Gly Pro Leu Val Arg Leu Leu Gly Val
255                 260                 265                 270

cat ggc ccc tgg ctg ccc ttg ctg gtg tat ggg acg gtg cca gtg ctg      1584
His Gly Pro Trp Leu Pro Leu Leu Val Tyr Gly Thr Val Pro Val Leu
                275                 280                 285

agt ggc ctg gcc gca ctg ctt ctg ccc gag acc cag agc ttg ccg ctg      1632
Ser Gly Leu Ala Ala Leu Leu Leu Pro Glu Thr Gln Ser Leu Pro Leu
            290                 295                 300

ccc gac acc atc caa gat gtg cag aac cag gca gta aag aag gca aca      1680
Pro Asp Thr Ile Gln Asp Val Gln Asn Gln Ala Val Lys Lys Ala Thr
        305                 310                 315

cat ggc acg ctg ggg aac tct gtc cta aaa tcc aca cag ttt              1722
His Gly Thr Leu Gly Asn Ser Val Leu Lys Ser Thr Gln Phe
    320                 325                 330

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agaaggcagg aggaaagcaa agacctccat ttccagaggc ccagaggctg ccctctgagg   1842

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ggcccccttc aatactgaag gggaaaagga cagtttgatt ggcaggaggt gacccagtgc   1962

accatcaccc tgccctgccc tcgtggcttc ggagagcaga ggggtcaggc ccaggggaac   2022

gagctggcct tgccaaccct ctgcttgact ccgcactgcc acttgtcccc ccacacccgt   2082

ccacctgccc agagctcaga gctaaccacc atccatggtc aagacctctc ctagctccac   2142

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35 40 45

Phe Leu Cys Phe Leu Tyr Ser Trp Trp Leu Ala Glu Ser Ala Arg Trp
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Leu Leu Thr Thr Gly Arg Leu Asp Trp Gly Leu Gln Glu Leu Trp Arg
65 70 75 80

Val Ala Ala Ile Asn Gly Lys Gly Ala Val Gln Asp Thr Leu Thr Pro
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Glu Val Leu Leu Ser Ala Met Arg Glu Glu Leu Ser Met Gly Gln Pro
100 105 110

Pro Ala Ser Leu Gly Thr Leu Leu Arg Met Pro Gly Leu Arg Phe Arg
115 120 125

Thr Cys Ile Ser Thr Leu Cys Trp Phe Ala Phe Gly Phe Thr Phe Phe
130 135 140

Gly Leu Ala Leu Asp Leu Gln Ala Leu Gly Ser Asn Ile Phe Leu Leu
145 150 155 160

Gln Met Phe Ile Gly Val Val Asp Ile Pro Ala Lys Met Gly Ala Leu
165 170 175

Leu Leu Leu Ser His Leu Gly Arg Arg Pro Thr Leu Ala Ala Ser Leu
180 185 190

Leu Leu Ala Gly Leu Cys Ile Leu Ala Asn Thr Leu Val Pro His Glu
195 200 205

Met Gly Ala Leu Arg Ser Ala Leu Ala Val Leu Gly Leu Gly Gly Val
210 215 220

Gly Ala Ala Phe Thr Cys Ile Thr Ile Tyr Ser Ser Glu Leu Phe Pro
225 230 235 240

DOCID: <WO 03089583A2 I >

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Thr Val Leu Arg Met Thr Ala Val Gly Leu Gly Gln Met Ala Ala Arg
                245                 250                 255

Gly Gly Ala Ile Leu Gly Pro Leu Val Arg Leu Leu Gly Val His Gly
            260                 265                 270

Pro Trp Leu Pro Leu Leu Val Tyr Gly Thr Val Pro Val Leu Ser Gly
        275                 280                 285

Leu Ala Ala Leu Leu Leu Pro Glu Thr Gln Ser Leu Pro Leu Pro Asp
    290                 295                 300

Thr Ile Gln Asp Val Gln Asn Gln Ala Val Lys Lys Ala Thr His Gly
305                 310                 315                 320

Thr Leu Gly Asn Ser Val Leu Lys Ser Thr Gln Phe
                325                 330
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<210> 80
<211> 2250
<212> DNA
<213> Homo sapiens

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<222> (10)..(738)
<223>

<400> 80

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caaggcagc atg agc cga tca ccc ctc aat ccc agc caa ctc cga tca gtg     51
          Met Ser Arg Ser Pro Leu Asn Pro Ser Gln Leu Arg Ser Val
          1               5                   10

ggc tcc cag gat gcc ctg gcc ccc ttg cct cca cct gct ccc cag aat       99
Gly Ser Gln Asp Ala Leu Ala Pro Leu Pro Pro Pro Ala Pro Gln Asn
15                  20                  25                  30

ccc tcc acc cac tct tgg gac cct ttg tgt gga tct ctg cct tgg ggc      147
Pro Ser Thr His Ser Trp Asp Pro Leu Cys Gly Ser Leu Pro Trp Gly
                35                  40                  45

ctc agc tgt ctt ctg gct ctg cag cat gtc ttg gtc atg gct tct ctg      195
Leu Ser Cys Leu Leu Ala Leu Gln His Val Leu Val Met Ala Ser Leu
            50                  55                  60

ctc tgt gtc tcc cac ctg ctc ctg ctt tgc agt ctc tcc cca gga gga      243
Leu Cys Val Ser His Leu Leu Leu Leu Cys Ser Leu Ser Pro Gly Gly
        65                  70                  75

ctc tct tac tcc cct tct cag ctc ctg gcc tcc agc ttc ttt tca tgt      291
Leu Ser Tyr Ser Pro Ser Gln Leu Leu Ala Ser Ser Phe Phe Ser Cys
    80                  85                  90

ggt atg tct acc atc ctg caa act tgg atg ggc agc agg ctg cct ctt      339
Gly Met Ser Thr Ile Leu Gln Thr Trp Met Gly Ser Arg Leu Pro Leu
95                  100                 105                 110

gtc cag gct cca tcc tta gag ttc ctt atc cct gct ctg gtg ctg acc      387
Val Gln Ala Pro Ser Leu Glu Phe Leu Ile Pro Ala Leu Val Leu Thr
                115                 120                 125

agc cag aag cta ccc cgg gcc atc cag aca cct gga aac tcc tcc ctc      435
Ser Gln Lys Leu Pro Arg Ala Ile Gln Thr Pro Gly Asn Ser Ser Leu
            130                 135                 140

atg ctg cac ctt tgt agg gga cct agc tgc cat ggc ctg ggg cac tgg      483
Met Leu His Leu Cys Arg Gly Pro Ser Cys His Gly Leu Gly His Trp
        145                 150                 155

aac act tct ctc cag gag gtg tcc ggg gca gtg gta gta tct ggg ctg      531
Asn Thr Ser Leu Gln Glu Val Ser Gly Ala Val Val Val Ser Gly Leu
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DOCID: <WO_____ 03089583A2_I_>

160 200 PCT FINAL.ST25

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    160                 165                 170

ctg cag ggc atg atg ggg ctg ctg ggg agt ccc ggc cac gtg ttc ccc      579
Leu Gln Gly Met Met Gly Leu Leu Gly Ser Pro Gly His Val Phe Pro
175                 180                 185                 190

cac tgt ggg ccc ctg gtg ctg gct ccc agc ctg gtt gtg gca ggg ctc      627
His Cys Gly Pro Leu Val Leu Ala Pro Ser Leu Val Val Ala Gly Leu
                195                 200                 205

tct gcc cac agg gag gta gcc cag ttc tgc ttc aca cac tgg ggg ttg      675
Ser Ala His Arg Glu Val Ala Gln Phe Cys Phe Thr His Trp Gly Leu
            210                 215                 220

gcc ttg ctg tac gtg agt cct gag agg cgt ggg atg gtg ccc agt ggg      723
Ala Leu Leu Tyr Val Ser Pro Glu Arg Arg Gly Met Val Pro Ser Gly
        225                 230                 235

ggt gta tgg ggg gac taggggaggg cagaactgct ggtcctatca gattcagcag      778
Gly Val Trp Gly Asp
    240

cgactggaat agggacatat tttatatttg gaatccaaga cttttccttg attcatctgg    838

tctccttgaa tttcacactg ttttctgctg tcccccaagg tcacttccta ttccttccat    898

gggagtttcc ttctctggta tcaccccccg ctcttatgat attctgccca ctcccacctc    958

ctttcccatc cctcaggata cccactgcct cttgctccta aagccttctg tctcctaggg   1018

ttatcctgct catggtggtc tgttctcagc acctgggctc ctgccagttt catgtgtgcc   1078

cctggaggcg agcttcaacg tcatcaactc acactcctct ccctgtcttc cggctccttt   1138

cggtatgtgt gggtctgggc agggcagtag aggtcagaag ggctggcctg gagtgctcac   1198

tccatccccc acctttttggc ttctgtctac ccctgcaagg ctggctcaga aggttctggg   1258

ggaggagttc ttttctcagt ctcgcccctc aggtgctgat cccagtggcc tgtgtgtgga   1318

ttgtttctgc ctttgtggga ttcagtgtta tcccccagga actgtctgcc cccaccaagg   1378

caccatggat ttggctgcct cacccaggtg agtggaattg gcctttgctg acgcccagag   1438

ctctggctgc aggcatctcc atggccttgg cagcctccac cagttccctg ggctgctatg   1498

ccctgtgtgg ccggctgctg catttgcctc ccccacctcc acatgcctgc agtcgagggc   1558

tgagcctgga ggggctgggc agtgtgctgg ccgggctgct gggaagcccc atgggcactg   1618

catccagctt ccccaacgtg ggcaaagtgg gtcttatcca ggtacgtgga cctgggatgg   1678

gagtggggta ggatggagct agaggggaag aagaaggaca ggaacttaca ccgattgatt   1738

gccaggtgtg cctagcacct cacatcaact atcttacttg gggaggtgcc taagattaga   1798

ctttgggcta agagagtggg gaagtgaaca aatcaccacg gaactcctgt gcatgaggca   1858

ctgtatcaag gctagggcaa agaaccagtc acataaagtt ctgctctctt ggggacttca   1918

tagagggaga ggcagacagt tgaaggaaaa aagtatcttt ttaaaaaagt gggccaggca   1978

tggtggctca cacctgtaat cctagcacgt ggggaggctg aggcaggcag atcacttagg   2038

ctaggaattc aagaccagcc tggccaacat ggtgaaaccc tgtctctact aaaaatacaa   2098

aaattagctg ggcatggtgt tgtgcaccta taattccagc tactcaggag gctgaggcag   2158

gagaatcgct tgagcctggg aggcagaggt tgctgtgagc cgagaccgca ccactgcact   2218

ccagcctggg cgacagagcg agactccatc tc                                 2250
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<210> 81
<211> 243
<212> PRT
<213> Homo sapiens

<400> 81

DOCID: <WO 03089583A2 I_>

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Met Ser Arg Ser Pro Leu Asn Pro Ser Gln Leu Arg Ser Val Gly Ser
1               5                   10                  15

Gln Asp Ala Leu Ala Pro Leu Pro Pro Pro Ala Pro Gln Asn Pro Ser
            20                  25                  30

Thr His Ser Trp Asp Pro Leu Cys Gly Ser Leu Pro Trp Gly Leu Ser
        35                  40                  45

Cys Leu Leu Ala Leu Gln His Val Leu Val Met Ala Ser Leu Leu Cys
    50                  55                  60

Val Ser His Leu Leu Leu Leu Cys Ser Leu Ser Pro Gly Gly Leu Ser
65                  70                  75                  80

Tyr Ser Pro Ser Gln Leu Leu Ala Ser Ser Phe Phe Ser Cys Gly Met
                85                  90                  95

Ser Thr Ile Leu Gln Thr Trp Met Gly Ser Arg Leu Pro Leu Val Gln
            100                 105                 110

Ala Pro Ser Leu Glu Phe Leu Ile Pro Ala Leu Val Leu Thr Ser Gln
        115                 120                 125

Lys Leu Pro Arg Ala Ile Gln Thr Pro Gly Asn Ser Ser Leu Met Leu
    130                 135                 140

His Leu Cys Arg Gly Pro Ser Cys His Gly Leu Gly His Trp Asn Thr
145                 150                 155                 160

Ser Leu Gln Glu Val Ser Gly Ala Val Val Val Ser Gly Leu Leu Gln
                165                 170                 175

Gly Met Met Gly Leu Leu Gly Ser Pro Gly His Val Phe Pro His Cys
            180                 185                 190

Gly Pro Leu Val Leu Ala Pro Ser Leu Val Val Ala Gly Leu Ser Ala
        195                 200                 205

His Arg Glu Val Ala Gln Phe Cys Phe Thr His Trp Gly Leu Ala Leu
    210                 215                 220

Leu Tyr Val Ser Pro Glu Arg Arg Gly Met Val Pro Ser Gly Gly Val
225                 230                 235                 240

Trp Gly Asp
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<210> 82
<211> 1865
<212> DNA
<213> Homo sapiens

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<221> CDS
<222> (99)..(1508)
<223>

<400> 82
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ttgtaattta tatagaattt taaaactctt caattaca atg gat aga ggg gag aaa 116

16U 200 PCT FINAL.ST25

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                                          Met Asp Arg Gly Glu Lys
                                          1               5

ata cag ctc aag aga gtg ttt gga tat tgg tgg ggc aca agt ttt ttg      164
Ile Gln Leu Lys Arg Val Phe Gly Tyr Trp Trp Gly Thr Ser Phe Leu
            10                  15                  20

ctt att aat atc att ggt gca gga att ttt gtg tcc ccc aaa ggt gtg      212
Leu Ile Asn Ile Ile Gly Ala Gly Ile Phe Val Ser Pro Lys Gly Val
        25                  30                  35

ttg gca tac tct tgc atg aac gtg gga gtc tcc ctg tgc gtt tgg gct      260
Leu Ala Tyr Ser Cys Met Asn Val Gly Val Ser Leu Cys Val Trp Ala
    40                  45                  50

ggc tgt gcc ata ctg gcc atg aca tca act ctt tgc tct gca gag ata      308
Gly Cys Ala Ile Leu Ala Met Thr Ser Thr Leu Cys Ser Ala Glu Ile
55                  60                  65                  70

agt ata agc ttc cca tgc agt gga gct caa tac tat ttt ctc aag aga      356
Ser Ile Ser Phe Pro Cys Ser Gly Ala Gln Tyr Tyr Phe Leu Lys Arg
                75                  80                  85

tac ttt ggc tcc acg gtt gct ttt ttg aat ctc tgg aca tcc ttg ttt      404
Tyr Phe Gly Ser Thr Val Ala Phe Leu Asn Leu Trp Thr Ser Leu Phe
            90                  95                  100

ctg ggg tca ggg gta gtt gct ggc caa gct ctg ctc ctt gct gag tac      452
Leu Gly Ser Gly Val Val Ala Gly Gln Ala Leu Leu Leu Ala Glu Tyr
        105                 110                 115

agc atc cag cct ttt ttt ccc agc tgc tct gtc cca aag ctg cct aag      500
Ser Ile Gln Pro Phe Phe Pro Ser Cys Ser Val Pro Lys Leu Pro Lys
    120                 125                 130

aaa tgt ctg gca ttg gcc atg ttg tgg att gta gga att ctg act tct      548
Lys Cys Leu Ala Leu Ala Met Leu Trp Ile Val Gly Ile Leu Thr Ser
135                 140                 145                 150

cgt ggt gtg aaa gaa gtg act tgg ctt cag ata gct agc tca gtg ctg      596
Arg Gly Val Lys Glu Val Thr Trp Leu Gln Ile Ala Ser Ser Val Leu
                155                 160                 165

aaa gtg tcc ata ctt agc ttc att tcc cta act gga gta gtg ttc ctg      644
Lys Val Ser Ile Leu Ser Phe Ile Ser Leu Thr Gly Val Val Phe Leu
            170                 175                 180

ata aga ggg aaa aag gag aat gta gaa cga ttt cag aat gct ttt gat      692
Ile Arg Gly Lys Lys Glu Asn Val Glu Arg Phe Gln Asn Ala Phe Asp
        185                 190                 195

gct gaa ctt cca gat atc tct cac ctt ata caa gcc atc ttc caa gga      740
Ala Glu Leu Pro Asp Ile Ser His Leu Ile Gln Ala Ile Phe Gln Gly
    200                 205                 210

tat ttt gca tat tca ggc ggg gca tgc ttt aca ctt ata gca ggg gag      788
Tyr Phe Ala Tyr Ser Gly Gly Ala Cys Phe Thr Leu Ile Ala Gly Glu
215                 220                 225                 230

ctg aag aag ccc aga aca aca att ccc aaa tgc ata ttt act gcg tta      836
Leu Lys Lys Pro Arg Thr Thr Ile Pro Lys Cys Ile Phe Thr Ala Leu
                235                 240                 245

cct ctg gtg act gta gtt tat tta ctg gtt aac att tcc tat ctg act      884
Pro Leu Val Thr Val Val Tyr Leu Leu Val Asn Ile Ser Tyr Leu Thr
            250                 255                 260

gtt ctg aca ccc agg gaa att ctc tct tca gat gct gta gct atc aca      932
Val Leu Thr Pro Arg Glu Ile Leu Ser Ser Asp Ala Val Ala Ile Thr
        265                 270                 275

tgg gct gat cga gct ttt ccc tca tta gca tgg att atg cct ttt gct      980
Trp Ala Asp Arg Ala Phe Pro Ser Leu Ala Trp Ile Met Pro Phe Ala
    280                 285                 290

att tct acc tca tta ttt agc aac ctt ctg att tct ata ttt aaa tca     1028
Ile Ser Thr Ser Leu Phe Ser Asn Leu Leu Ile Ser Ile Phe Lys Ser
295                 300                 305                 310
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IOCID: <WO_____03089583A2_I_>

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tcg aga cca ata tat ctt gca agc caa gag ggc cag ctg cct ttg cta     1076
Ser Arg Pro Ile Tyr Leu Ala Ser Gln Glu Gly Gln Leu Pro Leu Leu
                315                 320                 325

ttt aat aca ctt aat agt cac tct tct cca ttt aca gct gtg cta cta     1124
Phe Asn Thr Leu Asn Ser His Ser Ser Pro Phe Thr Ala Val Leu Leu
            330                 335                 340

ctt gtc act ttg gga tcc ctt gca att atc tta aca agt cta att gat     1172
Leu Val Thr Leu Gly Ser Leu Ala Ile Ile Leu Thr Ser Leu Ile Asp
        345                 350                 355

ttg ata aac tat att ttt ttc acg ggt tca tta tgg tct ata tta tta     1220
Leu Ile Asn Tyr Ile Phe Phe Thr Gly Ser Leu Trp Ser Ile Leu Leu
    360                 365                 370

atg ata gga ata cta agg cgg aga tac cag gaa ccc aat cta tct ata     1268
Met Ile Gly Ile Leu Arg Arg Arg Tyr Gln Glu Pro Asn Leu Ser Ile
375                 380                 385                 390

cct tat aag gtg ttt ttg tca ttt cca tta gca aca ata gtc atc gac     1316
Pro Tyr Lys Val Phe Leu Ser Phe Pro Leu Ala Thr Ile Val Ile Asp
                395                 400                 405

gtg ggc ttg gtt gtg ata cca ttg gta aag tct cca aat gtg cat tat     1364
Val Gly Leu Val Val Ile Pro Leu Val Lys Ser Pro Asn Val His Tyr
            410                 415                 420

gtc tac gtg ctt ctg tta gtt ctc agc gga tta cta ttt tac ata cct     1412
Val Tyr Val Leu Leu Leu Val Leu Ser Gly Leu Leu Phe Tyr Ile Pro
        425                 430                 435

tta ata cat ttt aaa ata aga ttg gct tgg ttt gag aag atg act tgc     1460
Leu Ile His Phe Lys Ile Arg Leu Ala Trp Phe Glu Lys Met Thr Cys
    440                 445                 450

tat tta caa tta cta ttt aat att tgc ctc cct gat gtg tct gag gaa     1508
Tyr Leu Gln Leu Leu Phe Asn Ile Cys Leu Pro Asp Val Ser Glu Glu
455                 460                 465                 470

tagatgtcgg aagtgcaaac tcttaaaaaa ttggccttct aaaaaacata tatcagattc   1568

caaatcaagg ttaaacatat gatagaacat tcatggtgaa attcctatgg taaatatttt   1628

tttctcaaat gaaataagta atgtatacaa aagtgcctaa gacagtacct ggcttcagag   1688

tcactaagaa attgctaaaa gctctgcttc gcatggtaaa aaacttaagt cctggtttgc   1748

gtagcttgat agagtgatta tacaacttcc attctctcac ttttttttc tgtatcccac   1808

ccctttttcta ctgaatttgt ggggatccta taataaaagt gaatgactaa aaatttt     1865
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<210> 83
<211> 470
<212> PRT
<213> Homo sapiens

<400> 83

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Met Asp Arg Gly Glu Lys Ile Gln Leu Lys Arg Val Phe Gly Tyr Trp
1               5                   10                  15

Trp Gly Thr Ser Phe Leu Leu Ile Asn Ile Ile Gly Ala Gly Ile Phe
            20                  25                  30

Val Ser Pro Lys Gly Val Leu Ala Tyr Ser Cys Met Asn Val Gly Val
        35                  40                  45

Ser Leu Cys Val Trp Ala Gly Cys Ala Ile Leu Ala Met Thr Ser Thr
    50                  55                  60

Leu Cys Ser Ala Glu Ile Ser Ile Ser Phe Pro Cys Ser Gly Ala Gln
65                  70                  75                  80
```


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Tyr Tyr Phe Leu Lys Arg Tyr Phe Gly Ser Thr Val Ala Phe Leu Asn
85 90 95

Leu Trp Thr Ser Leu Phe Leu Gly Ser Gly Val Val Ala Gly Gln Ala
100 105 110

Leu Leu Leu Ala Glu Tyr Ser Ile Gln Pro Phe Phe Pro Ser Cys Ser
115 120 125

Val Pro Lys Leu Pro Lys Lys Cys Leu Ala Leu Ala Met Leu Trp Ile
130 135 140

Val Gly Ile Leu Thr Ser Arg Gly Val Lys Glu Val Thr Trp Leu Gln
145 150 155 160

Ile Ala Ser Ser Val Leu Lys Val Ser Ile Leu Ser Phe Ile Ser Leu
165 170 175

Thr Gly Val Val Phe Leu Ile Arg Gly Lys Lys Glu Asn Val Glu Arg
180 185 190

Phe Gln Asn Ala Phe Asp Ala Glu Leu Pro Asp Ile Ser His Leu Ile
195 200 205

Gln Ala Ile Phe Gln Gly Tyr Phe Ala Tyr Ser Gly Gly Ala Cys Phe
210 215 220

Thr Leu Ile Ala Gly Glu Leu Lys Lys Pro Arg Thr Thr Ile Pro Lys
225 230 235 240

Cys Ile Phe Thr Ala Leu Pro Leu Val Thr Val Val Tyr Leu Leu Val
245 250 255

Asn Ile Ser Tyr Leu Thr Val Leu Thr Pro Arg Glu Ile Leu Ser Ser
260 265 270

Asp Ala Val Ala Ile Thr Trp Ala Asp Arg Ala Phe Pro Ser Leu Ala
275 280 285

Trp Ile Met Pro Phe Ala Ile Ser Thr Ser Leu Phe Ser Asn Leu Leu
290 295 300

Ile Ser Ile Phe Lys Ser Ser Arg Pro Ile Tyr Leu Ala Ser Gln Glu
305 310 315 320

Gly Gln Leu Pro Leu Leu Phe Asn Thr Leu Asn Ser His Ser Ser Pro
325 330 335

Phe Thr Ala Val Leu Leu Leu Val Thr Leu Gly Ser Leu Ala Ile Ile
340 345 350

Leu Thr Ser Leu Ile Asp Leu Ile Asn Tyr Ile Phe Phe Thr Gly Ser
355 360 365

Leu Trp Ser Ile Leu Leu Met Ile Gly Ile Leu Arg Arg Arg Tyr Gln
370 375 380

Glu Pro Asn Leu Ser Ile Pro Tyr Lys Val Phe Leu Ser Phe Pro Leu
385 390 395 400

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Ala Thr Ile Val Ile Asp Val Gly Leu Val Val Ile Pro Leu Val Lys
                405                 410                 415

Ser Pro Asn Val His Tyr Val Tyr Val Leu Leu Leu Val Leu Ser Gly
            420                 425                 430

Leu Leu Phe Tyr Ile Pro Leu Ile His Phe Lys Ile Arg Leu Ala Trp
        435                 440                 445

Phe Glu Lys Met Thr Cys Tyr Leu Gln Leu Leu Phe Asn Ile Cys Leu
    450                 455                 460

Pro Asp Val Ser Glu Glu
465                 470


<210>  84
<211>  1046
<212>  DNA
<213>  Homo sapiens

<220>
<221>  CDS
<222>  (319)..(852)
<223>

<400>  84
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gctagggtca gatttcaaat tctcatctct tggtgccaat accaccacca gattcttctt    120

tgaagtcaac ttttgagatc ttcactaagt acacgttggt gtctgaagat tcacacgagt    180

gcctctggta atcattttct tcagggaatc acagtctctc ctctcagcaa agcatccact    240

gtactgaact ttgcttttgg aaacatcttc ttcctgagac ctcgttgaaa gaaactctct    300

ggtgtcatac tttccaat atg gag gtg aag aac ttt gca gtt tgg gat tat      351
                    Met Glu Val Lys Asn Phe Ala Val Trp Asp Tyr
                    1               5                   10

gtt gta ttt gca gcc ctc ttt ttc att tcc tct gga att ggg gtg ttc      399
Val Val Phe Ala Ala Leu Phe Phe Ile Ser Ser Gly Ile Gly Val Phe
            15                  20                  25

ttt gcc att aag gag aga aaa aag gca act tcc cga gag ttc ctg gtt      447
Phe Ala Ile Lys Glu Arg Lys Lys Ala Thr Ser Arg Glu Phe Leu Val
        30                  35                  40

ggg gga agg caa atg agc ttt ggc cct gtc ggc ttg tct ctg aca gcc      495
Gly Gly Arg Gln Met Ser Phe Gly Pro Val Gly Leu Ser Leu Thr Ala
    45                  50                  55

agc ttc atg tca gct gtc acg gtc ctg ggg acc cct tct gaa gtc tac      543
Ser Phe Met Ser Ala Val Thr Val Leu Gly Thr Pro Ser Glu Val Tyr
60                  65                  70                  75

cgc ttt ggg gca tcc ttc cta gtc ttc ttc att gct tac cta ttt gtc      591
Arg Phe Gly Ala Ser Phe Leu Val Phe Phe Ile Ala Tyr Leu Phe Val
                80                  85                  90

atc ctc tta aca tca gag ctc ttt ctc cct gtg ttc tac aga tct ggt      639
Ile Leu Leu Thr Ser Glu Leu Phe Leu Pro Val Phe Tyr Arg Ser Gly
            95                  100                 105

atc acc agc act tat gag tac tta caa cta cga ttc aac aaa cca gtt      687
Ile Thr Ser Thr Tyr Glu Tyr Leu Gln Leu Arg Phe Asn Lys Pro Val
        110                 115                 120

cgc tat gct gcc acg gtc atc tac att gta cag acg att ctc tac aca      735
Arg Tyr Ala Ala Thr Val Ile Tyr Ile Val Gln Thr Ile Leu Tyr Thr
    125                 130                 135
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gga gtg gtg gtg tat gct cct gcc ctg gca ctc aat caa gtg act ggg      783
Gly Val Val Val Tyr Ala Pro Ala Leu Ala Leu Asn Gln Val Thr Gly
140                 145                 150                 155

ttt gat ctc tgg ggc tct gtg ttt gca aca gga att gtt tgc aca ttc      831
Phe Asp Leu Trp Gly Ser Val Phe Ala Thr Gly Ile Val Cys Thr Phe
                160                 165                 170

tac tgt acc ctg gta tgt atc tagctgtgaa gaagtattta acactacctc        882
Tyr Cys Thr Leu Val Cys Ile
            175

ctaatatggg ataagggcaa atctccagca ataggcatct aattatagca gaattcgtta    942

ttccaaaatt aagcagaagt atgtcggctt atctgtcaca gtttcctgag gaaggtgctg   1002

ttgtttaaca ttctttttcat taccaacctt taggagaatt taat                   1046
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<210> 85
<211> 178
<212> PRT
<213> Homo sapiens

<400> 85

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Met Glu Val Lys Asn Phe Ala Val Trp Asp Tyr Val Val Phe Ala Ala
1               5                   10                  15

Leu Phe Phe Ile Ser Ser Gly Ile Gly Val Phe Phe Ala Ile Lys Glu
            20                  25                  30

Arg Lys Lys Ala Thr Ser Arg Glu Phe Leu Val Gly Gly Arg Gln Met
        35                  40                  45

Ser Phe Gly Pro Val Gly Leu Ser Leu Thr Ala Ser Phe Met Ser Ala
    50                  55                  60

Val Thr Val Leu Gly Thr Pro Ser Glu Val Tyr Arg Phe Gly Ala Ser
65                  70                  75                  80

Phe Leu Val Phe Phe Ile Ala Tyr Leu Phe Val Ile Leu Leu Thr Ser
                85                  90                  95

Glu Leu Phe Leu Pro Val Phe Tyr Arg Ser Gly Ile Thr Ser Thr Tyr
            100                 105                 110

Glu Tyr Leu Gln Leu Arg Phe Asn Lys Pro Val Arg Tyr Ala Ala Thr
        115                 120                 125

Val Ile Tyr Ile Val Gln Thr Ile Leu Tyr Thr Gly Val Val Val Tyr
    130                 135                 140

Ala Pro Ala Leu Ala Leu Asn Gln Val Thr Gly Phe Asp Leu Trp Gly
145                 150                 155                 160

Ser Val Phe Ala Thr Gly Ile Val Cys Thr Phe Tyr Cys Thr Leu Val
                165                 170                 175

Cys Ile
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<210> 86
<211> 4751
<212> DNA
<213> Homo sapiens

OCID: <WO_____03089583A2_I_>

<220>
<221> CDS
<222> (382)..(1929)
<223>

<400> 86
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ttccgcgcta cgcttccctc tcccggcgtt gccagctagg cccccggccc cagcctcgcc 120

ggcgcctccg cccagtccgc tccccgcccc accgaagcgc ggatcgcgca gcctggggcc 180

cgggaagggg ccactgcgca gggacgcggc tcggcgggtg cgccccgggg gcatgtccgc 240

gcgctaccgc cagggctgca gtggtcccgg cgaggccctg gcaaccacca ttctactttt 300

tgtgtctatg agtttgacta ccctaaggac ctcacatggc gagtaaccca tgggccaggt 360

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Met Pro Ser Gly Ser His Trp Thr Ala Asn
1 5 10

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Ser Ser Lys Ile Ile Thr Trp Leu Leu Glu Gln Pro Gly Lys Glu Glu
15 20 25

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Lys Arg Lys Thr Met Ala Lys Val Asn Arg Ala Arg Ser Thr Ser Pro
30 35 40

cca gat gga ggc tgg ggc tgg atg att gtg gct ggc tgt ttc ctt gtt 555
Pro Asp Gly Gly Trp Gly Trp Met Ile Val Ala Gly Cys Phe Leu Val
45 50 55

acc atc tgc aca cgg gca gtc aca aga tgt atc tca att ttt ttt gtg 603
Thr Ile Cys Thr Arg Ala Val Thr Arg Cys Ile Ser Ile Phe Phe Val
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gag ttc cag aca tac ttc act cag gat tac gca caa acg gca tgg atc 651
Glu Phe Gln Thr Tyr Phe Thr Gln Asp Tyr Ala Gln Thr Ala Trp Ile
75 80 85 90

cat tcc att gta gat tgt gtg acc atg ctc tgt gct cca ctt ggg agt 699
His Ser Ile Val Asp Cys Val Thr Met Leu Cys Ala Pro Leu Gly Ser
95 100 105

gtt gtc agt aac cat tta tcc tgt caa gtg gga atc atg ctg ggt ggc 747
Val Val Ser Asn His Leu Ser Cys Gln Val Gly Ile Met Leu Gly Gly
110 115 120

ttg ctt gca tct act gga ctc atc ctg agc tca ttt gcc acg agt ctg 795
Leu Leu Ala Ser Thr Gly Leu Ile Leu Ser Ser Phe Ala Thr Ser Leu
125 130 135

aag cat ctc tac ctc act ctg gga gtt ctt aca ggt ctt gga ttt gca 843
Lys His Leu Tyr Leu Thr Leu Gly Val Leu Thr Gly Leu Gly Phe Ala
140 145 150

ctt tgt tac tct cca gct att gcc atg gtt ggc aag tac ttc agc aga 891
Leu Cys Tyr Ser Pro Ala Ile Ala Met Val Gly Lys Tyr Phe Ser Arg
155 160 165 170

cgg aaa gcc ctt gct tat ggt atc gcc atg tca gga agt ggc att ggc 939
Arg Lys Ala Leu Ala Tyr Gly Ile Ala Met Ser Gly Ser Gly Ile Gly
175 180 185

acc ttc atc ctg gct cct gtg gtt cag ctc ctt att gaa cag ttt tcc 987
Thr Phe Ile Leu Ala Pro Val Val Gln Leu Leu Ile Glu Gln Phe Ser
190 195 200

tgg cgg gga gcc tta ctc att ctt ggg ggc ttt gtc ttg aat ctc tgt 1035
Trp Arg Gly Ala Leu Leu Ile Leu Gly Gly Phe Val Leu Asn Leu Cys
205 210 215

gta tgt ggt gcc ttg atg agg cca att act ctt aaa gag gac cac aca 1083
Val Cys Gly Ala Leu Met Arg Pro Ile Thr Leu Lys Glu Asp His Thr
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act cca gag cag aac cat gtg tgt aga act cag aaa gaa gac att aag 1131

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Arg Val Ser Pro Tyr Ser Ser Leu Thr Lys Glu Trp Ala Gln Thr Cys
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ctc tgt tgc tgt ttg cag caa gag tac agt ttt tta ctc atg tca gac     1227
Leu Cys Cys Cys Leu Gln Gln Glu Tyr Ser Phe Leu Leu Met Ser Asp
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ttt gtt gtg tta gcc gtc tcc gtt ctg ttt atg gct tat ggc tgc agc     1275
Phe Val Val Leu Ala Val Ser Val Leu Phe Met Ala Tyr Gly Cys Ser
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cct ctc ttt gtg tac ttg gtg cct tat gct ttg agt gtt gga gtg agt     1323
Pro Leu Phe Val Tyr Leu Val Pro Tyr Ala Leu Ser Val Gly Val Ser
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cat cag caa gct gct ttt ctt atg tcc ata ctt gga gtg att gac att     1371
His Gln Gln Ala Ala Phe Leu Met Ser Ile Leu Gly Val Ile Asp Ile
315                 320                 325                 330

att ggc aat atc aca ttt gga tgg ctg acc gac aga agg tgt ctg aag     1419
Ile Gly Asn Ile Thr Phe Gly Trp Leu Thr Asp Arg Arg Cys Leu Lys
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aat tac cag tat gtt tgc tac ctc ttt gcc gtg gga atg gat ggg ctc     1467
Asn Tyr Gln Tyr Val Cys Tyr Leu Phe Ala Val Gly Met Asp Gly Leu
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tgc tat ctc tgc ctc cca atg ctt caa agt ctc cct ctg ctc gtg cct     1515
Cys Tyr Leu Cys Leu Pro Met Leu Gln Ser Leu Pro Leu Leu Val Pro
        365                 370                 375

ttc tct tgt acc ttt ggc tac ttt gat ggt gcc tat gtg act ttg atc     1563
Phe Ser Cys Thr Phe Gly Tyr Phe Asp Gly Ala Tyr Val Thr Leu Ile
    380                 385                 390

cca gta gtg acc aca gag ata gtg ggg acc acc tct ttg tca tca gcg     1611
Pro Val Val Thr Thr Glu Ile Val Gly Thr Thr Ser Leu Ser Ser Ala
395                 400                 405                 410

ctt ggt gtg gta tac ttc ctt cac gca gtg cca tac ttg gtg agc cca     1659
Leu Gly Val Val Tyr Phe Leu His Ala Val Pro Tyr Leu Val Ser Pro
                415                 420                 425

ccc atc gca gga cgg ctg gta gat acc acc ggc agc tac act gca gca     1707
Pro Ile Ala Gly Arg Leu Val Asp Thr Thr Gly Ser Tyr Thr Ala Ala
            430                 435                 440

ttc ctc ctc tgt gga ttt tca atg ata ttt agt tct gtg ttg ctt ggc     1755
Phe Leu Leu Cys Gly Phe Ser Met Ile Phe Ser Ser Val Leu Leu Gly
        445                 450                 455

ttt gct aga ctt ata aag aga atg aga aaa acc cag ttg cag ttc att     1803
Phe Ala Arg Leu Ile Lys Arg Met Arg Lys Thr Gln Leu Gln Phe Ile
    460                 465                 470

gcc aaa gaa tct gat cct aag ctg cag cta tgg acc aat gga tca gtg     1851
Ala Lys Glu Ser Asp Pro Lys Leu Gln Leu Trp Thr Asn Gly Ser Val
475                 480                 485                 490

gct tat tct gtg gca aga gaa tta gat cag aaa cat ggg gag cct gtg     1899
Ala Tyr Ser Val Ala Arg Glu Leu Asp Gln Lys His Gly Glu Pro Val
                495                 500                 505

gct aca gca gtg cct ggc tac agc ctc aca tgaccaaagg ccttgagccc       1949
Ala Thr Ala Val Pro Gly Tyr Ser Leu Thr
            510                 515

cagaatcttc aggtttgaga gaggtggggc caccagattc ttcatgtttc tgaaactttt   2009

tattttggca gaaggattgc cttccaagga aattattatt attgttttgt taacatatta   2069

atatttataa gggaaaacag cacataataa ggaaagctgg actagcccag agccttctca   2129

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gattaatata gaaagaaact cttatttttt ttttctctta gtcttccagc cagcccttgc 2549

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35 40 45

Trp Met Ile Val Ala Gly Cys Phe Leu Val Thr Ile Cys Thr Arg Ala
50 55 60

Val Thr Arg Cys Ile Ser Ile Phe Phe Val Glu Phe Gln Thr Tyr Phe
65 70 75 80

Thr Gln Asp Tyr Ala Gln Thr Ala Trp Ile His Ser Ile Val Asp Cys
85 90 95

Val Thr Met Leu Cys Ala Pro Leu Gly Ser Val Val Ser Asn His Leu
100 105 110

Ser Cys Gln Val Gly Ile Met Leu Gly Gly Leu Leu Ala Ser Thr Gly
115 120 125

Leu Ile Leu Ser Ser Phe Ala Thr Ser Leu Lys His Leu Tyr Leu Thr
130 135 140

Leu Gly Val Leu Thr Gly Leu Gly Phe Ala Leu Cys Tyr Ser Pro Ala
145 150 155 160

Ile Ala Met Val Gly Lys Tyr Phe Ser Arg Arg Lys Ala Leu Ala Tyr
165 170 175

Gly Ile Ala Met Ser Gly Ser Gly Ile Gly Thr Phe Ile Leu Ala Pro
180 185 190

Val Val Gln Leu Leu Ile Glu Gln Phe Ser Trp Arg Gly Ala Leu Leu
195 200 205

Ile Leu Gly Gly Phe Val Leu Asn Leu Cys Val Cys Gly Ala Leu Met
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Arg Pro Ile Thr Leu Lys Glu Asp His Thr Thr Pro Glu Gln Asn His
225 230 235 240

Val Cys Arg Thr Gln Lys Glu Asp Ile Lys Arg Val Ser Pro Tyr Ser
245 250 255

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Gln Glu Tyr Ser Phe Leu Leu Met Ser Asp Phe Val Val Leu Ala Val
275 280 285

Ser Val Leu Phe Met Ala Tyr Gly Cys Ser Pro Leu Phe Val Tyr Leu
290 295 300

Val Pro Tyr Ala Leu Ser Val Gly Val Ser His Gln Gln Ala Ala Phe
305 310 315 320

Leu Met Ser Ile Leu Gly Val Ile Asp Ile Ile Gly Asn Ile Thr Phe
325 330 335

Gly Trp Leu Thr Asp Arg Arg Cys Leu Lys Asn Tyr Gln Tyr Val Cys
340 345 350

Tyr Leu Phe Ala Val Gly Met Asp Gly Leu Cys Tyr Leu Cys Leu Pro
355 360 365

Met Leu Gln Ser Leu Pro Leu Leu Val Pro Phe Ser Cys Thr Phe Gly
370 375 380

Tyr Phe Asp Gly Ala Tyr Val Thr Leu Ile Pro Val Val Thr Thr Glu
385 390 395 400

Ile Val Gly Thr Thr Ser Leu Ser Ser Ala Leu Gly Val Val Tyr Phe
405 410 415

Leu His Ala Val Pro Tyr Leu Val Ser Pro Pro Ile Ala Gly Arg Leu
420 425 430

Val Asp Thr Thr Gly Ser Tyr Thr Ala Ala Phe Leu Leu Cys Gly Phe
435 440 445

Ser Met Ile Phe Ser Ser Val Leu Leu Gly Phe Ala Arg Leu Ile Lys
450 455 460

Arg Met Arg Lys Thr Gln Leu Gln Phe Ile Ala Lys Glu Ser Asp Pro
465 470 475 480

Lys Leu Gln Leu Trp Thr Asn Gly Ser Val Ala Tyr Ser Val Ala Arg
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Tyr Ser Leu Thr
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   Met Asp Ser Leu Gln Asp Thr Val Ala Leu Asp His Gly Gly Cys
   1               5                  10                  15

tgc cct gcc ctc agc agg ctg gtt ccc aga ggc ttt ggg act gag atg      155
Cys Pro Ala Leu Ser Arg Leu Val Pro Arg Gly Phe Gly Thr Glu Met
                20                  25                  30

tgg act ctc ttt gcc ctt tct gga ccc ctg ttc ctg ttc cag gtg ctg      203
Trp Thr Leu Phe Ala Leu Ser Gly Pro Leu Phe Leu Phe Gln Val Leu
            35                  40                  45

act ttt atg atc tac atc gtg agc act gtg ttc tgc ggg cac ctg ggc      251
Thr Phe Met Ile Tyr Ile Val Ser Thr Val Phe Cys Gly His Leu Gly
        50                  55                  60

aag gtg gag ctg gca tcg gtg acc ctc gcg gtg gcc ttt gtc aat gtc      299
Lys Val Glu Leu Ala Ser Val Thr Leu Ala Val Ala Phe Val Asn Val
    65                  70                  75

tgc gga gtt tct gta gga gtt ggt ttg tct tcg gca tgt gac acc ttg      347
Cys Gly Val Ser Val Gly Val Gly Leu Ser Ser Ala Cys Asp Thr Leu
80                  85                  90                  95

atg tct cag agc ttc ggc agc ccc aac aag aag cac gtg ggc gtg atc      395
Met Ser Gln Ser Phe Gly Ser Pro Asn Lys Lys His Val Gly Val Ile
                100                 105                 110

ctg cag cgg ggc gcg ctg gtc ctg ctc ctc tgc tgc ctc cct tgc tgg      443
Leu Gln Arg Gly Ala Leu Val Leu Leu Leu Cys Cys Leu Pro Cys Trp
            115                 120                 125

gcg ctc ttc ctc aac acc cag cac atc ctg ctg ctc ttc cgg cag gac      491
Ala Leu Phe Leu Asn Thr Gln His Ile Leu Leu Leu Phe Arg Gln Asp
        130                 135                 140

ccg gac gtg tcc agg ttg acc cag gac tat gta atg att ttc att cca      539
Pro Asp Val Ser Arg Leu Thr Gln Asp Tyr Val Met Ile Phe Ile Pro
    145                 150                 155

gga ctt ccg gtg att ttt ctt tac aat ctg ctg gca aaa tat ttg caa      587
Gly Leu Pro Val Ile Phe Leu Tyr Asn Leu Leu Ala Lys Tyr Leu Gln
160                 165                 170                 175

aat cag aag atc acc tgg ccc caa gtc ctc agt ggt gtg gtg ggc aac      635
Asn Gln Lys Ile Thr Trp Pro Gln Val Leu Ser Gly Val Val Gly Asn
                180                 185                 190

tgt gtc aac ggt gtg gcc aac tat gcc ctg gtt tct gtg ctg aac ctg      683
Cys Val Asn Gly Val Ala Asn Tyr Ala Leu Val Ser Val Leu Asn Leu
            195                 200                 205

ggg gtc agg ggc tcc gcc tat gcc aac atc atc tcc cag ttt gca cag      731
Gly Val Arg Gly Ser Ala Tyr Ala Asn Ile Ile Ser Gln Phe Ala Gln
        210                 215                 220

acc gtc ttc ctc ctt ctc tac att gtg ctg aag aag ctg cac ctg gag      779
Thr Val Phe Leu Leu Leu Tyr Ile Val Leu Lys Lys Leu His Leu Glu
    225                 230                 235

acg tgg gca ggt tgg tcc agc cag tgc ctg cag gac tgg ggc ccc ttc      827
Thr Trp Ala Gly Trp Ser Ser Gln Cys Leu Gln Asp Trp Gly Pro Phe
240                 245                 250                 255

ttc tcc ctg gct gtc ccc agc atg ctc atg atc tgt gtt gag tgg tgg      875
Phe Ser Leu Ala Val Pro Ser Met Leu Met Ile Cys Val Glu Trp Trp
                260                 265                 270

gcc tat gag atc ggg agc ttc ctc atg ggg ctg ctc agt gtg gtg gat      923
Ala Tyr Glu Ile Gly Ser Phe Leu Met Gly Leu Leu Ser Val Val Asp
            275                 280                 285

ctc tct gcc cag gct gtc atc tac gag gtg gcc act gtg acc tac atg      971
Leu Ser Ala Gln Ala Val Ile Tyr Glu Val Ala Thr Val Thr Tyr Met
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Leu Gly Ala Ala Asp Thr Val Gln Ala Lys Arg Ser Ala Val Ser Gly
320                 325                 330                 335

gtg ctc agc ata gtt ggc att tcc ctg gtc ctg ggc acc ctg ata agc     1115
Val Leu Ser Ile Val Gly Ile Ser Leu Val Leu Gly Thr Leu Ile Ser
                340                 345                 350

atc ctg aaa aat cag ctg ggg cat att ttt acc aat gat gaa gat gtc     1163
Ile Leu Lys Asn Gln Leu Gly His Ile Phe Thr Asn Asp Glu Asp Val
            355                 360                 365

att gcc ctg gtg agc cag gtc ttg ccg gtt tat agt gtc ttt cac gtg     1211
Ile Ala Leu Val Ser Gln Val Leu Pro Val Tyr Ser Val Phe His Val
        370                 375                 380

ttt gag gcc atc tgt tgt gtc tat ggc gga gtt ctg aga gga act ggg     1259
Phe Glu Ala Ile Cys Cys Val Tyr Gly Gly Val Leu Arg Gly Thr Gly
    385                 390                 395

aag cag gcc ttt ggt gcc gct gtg aat gcc atc aca tat tac atc atc     1307
Lys Gln Ala Phe Gly Ala Ala Val Asn Ala Ile Thr Tyr Tyr Ile Ile
400                 405                 410                 415

ggc cta cca ctg ggc atc ctt ctg acc ttt gtg gtc aga atg aga atc     1355
Gly Leu Pro Leu Gly Ile Leu Leu Thr Phe Val Val Arg Met Arg Ile
                420                 425                 430

atg ggc ctc tgg ctg ggc atg ctg gcc tgt gtc ttc ctg gca act gct     1403
Met Gly Leu Trp Leu Gly Met Leu Ala Cys Val Phe Leu Ala Thr Ala
            435                 440                 445

gcc ttt gtt gct tat act gcc cgg ctg gac tgg aag ctt gct gca gag     1451
Ala Phe Val Ala Tyr Thr Ala Arg Leu Asp Trp Lys Leu Ala Ala Glu
        450                 455                 460

gag gct aag aaa cat tca ggc cgg cag cag cag cag aga gca gag agc     1499
Glu Ala Lys Lys His Ser Gly Arg Gln Gln Gln Gln Arg Ala Glu Ser
    465                 470                 475

act gca acc aga cct ggg cct gag aaa gca gtc cta tct tca gtg gct     1547
Thr Ala Thr Arg Pro Gly Pro Glu Lys Ala Val Leu Ser Ser Val Ala
480                 485                 490                 495

aca ggc agt tcc cct ggc att acc ttg aca acg tat tca agg tct gag     1595
Thr Gly Ser Ser Pro Gly Ile Thr Leu Thr Thr Tyr Ser Arg Ser Glu
                500                 505                 510

tgc cac gtg gac ttc ttc agg act cca gag gag gcc cac gcc ctt tca     1643
Cys His Val Asp Phe Phe Arg Thr Pro Glu Glu Ala His Ala Leu Ser
            515                 520                 525

gct cct acc agc aga cta tca gtg aaa cag ctg gtc atc cgc cgt ggg     1691
Ala Pro Thr Ser Arg Leu Ser Val Lys Gln Leu Val Ile Arg Arg Gly
        530                 535                 540

gct gct ctg ggg gcg gcg tca gcc aca ctg atg gtg ggg ctc acg gtc     1739
Ala Ala Leu Gly Ala Ala Ser Ala Thr Leu Met Val Gly Leu Thr Val
    545                 550                 555

agg atc cta gcc acc agg cac tagcaaagaa gcttggaaat agaaagccag       1790
Arg Ile Leu Ala Thr Arg His
560                 565

gagtggctgt ccccagtatg caaacacacc acggtctgcc ctgcaaaaac accaatgggg  1850

tctagtgcag gtggacactt tgaaccactc ctcaaaaaaa gaactttggc tgattccttg  1910

tggtgacact cagaggggtc tgaacagact tgacaattct gttctggtca agctggagtt  1970

ttcttctgtg acttggactg ctctacagaa gacatcagcc aactgcacga gtcagagtcc  2030

agggattgtc actattatta ataatgtaaa tggcttcaaa tgggacactg cagataaaat  2090

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35 40 45

Phe Met Ile Tyr Ile Val Ser Thr Val Phe Cys Gly His Leu Gly Lys
50 55 60

Val Glu Leu Ala Ser Val Thr Leu Ala Val Ala Phe Val Asn Val Cys
65 70 75 80

Gly Val Ser Val Gly Val Gly Leu Ser Ser Ala Cys Asp Thr Leu Met
85 90 95

Ser Gln Ser Phe Gly Ser Pro Asn Lys Lys His Val Gly Val Ile Leu
100 105 110

Gln Arg Gly Ala Leu Val Leu Leu Leu Cys Cys Leu Pro Cys Trp Ala
115 120 125

Leu Phe Leu Asn Thr Gln His Ile Leu Leu Leu Phe Arg Gln Asp Pro
130 135 140

Asp Val Ser Arg Leu Thr Gln Asp Tyr Val Met Ile Phe Ile Pro Gly
145 150 155 160

Leu Pro Val Ile Phe Leu Tyr Asn Leu Leu Ala Lys Tyr Leu Gln Asn
165 170 175

Gln Lys Ile Thr Trp Pro Gln Val Leu Ser Gly Val Val Gly Asn Cys
180 185 190

Val Asn Gly Val Ala Asn Tyr Ala Leu Val Ser Val Leu Asn Leu Gly
195 200 205

Val Arg Gly Ser Ala Tyr Ala Asn Ile Ile Ser Gln Phe Ala Gln Thr
210 215 220

Val Phe Leu Leu Leu Tyr Ile Val Leu Lys Lys Leu His Leu Glu Thr
225 230 235 240

Trp Ala Gly Trp Ser Ser Gln Cys Leu Gln Asp Trp Gly Pro Phe Phe
245 250 255

Ser Leu Ala Val Pro Ser Met Leu Met Ile Cys Val Glu Trp Trp Ala
260 265 270

Tyr Glu Ile Gly Ser Phe Leu Met Gly Leu Leu Ser Val Val Asp Leu
275 280 285

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Ser Ala Gln Ala Val Ile Tyr Glu Val Ala Thr Val Thr Tyr Met Ile
    290                 295                 300

Pro Leu Gly Leu Ser Ile Gly Val Cys Val Arg Val Gly Met Ala Leu
305                 310                 315                 320

Gly Ala Ala Asp Thr Val Gln Ala Lys Arg Ser Ala Val Ser Gly Val
                325                 330                 335

Leu Ser Ile Val Gly Ile Ser Leu Val Leu Gly Thr Leu Ile Ser Ile
            340                 345                 350

Leu Lys Asn Gln Leu Gly His Ile Phe Thr Asn Asp Glu Asp Val Ile
        355                 360                 365

Ala Leu Val Ser Gln Val Leu Pro Val Tyr Ser Val Phe His Val Phe
    370                 375                 380

Glu Ala Ile Cys Cys Val Tyr Gly Gly Val Leu Arg Gly Thr Gly Lys
385                 390                 395                 400

Gln Ala Phe Gly Ala Ala Val Asn Ala Ile Thr Tyr Tyr Ile Ile Gly
                405                 410                 415

Leu Pro Leu Gly Ile Leu Leu Thr Phe Val Val Arg Met Arg Ile Met
            420                 425                 430

Gly Leu Trp Leu Gly Met Leu Ala Cys Val Phe Leu Ala Thr Ala Ala
        435                 440                 445

Phe Val Ala Tyr Thr Ala Arg Leu Asp Trp Lys Leu Ala Ala Glu Glu
    450                 455                 460

Ala Lys Lys His Ser Gly Arg Gln Gln Gln Gln Arg Ala Glu Ser Thr
465                 470                 475                 480

Ala Thr Arg Pro Gly Pro Glu Lys Ala Val Leu Ser Ser Val Ala Thr
                485                 490                 495

Gly Ser Ser Pro Gly Ile Thr Leu Thr Thr Tyr Ser Arg Ser Glu Cys
            500                 505                 510

His Val Asp Phe Phe Arg Thr Pro Glu Glu Ala His Ala Leu Ser Ala
        515                 520                 525

Pro Thr Ser Arg Leu Ser Val Lys Gln Leu Val Ile Arg Arg Gly Ala
    530                 535                 540

Ala Leu Gly Ala Ala Ser Ala Thr Leu Met Val Gly Leu Thr Val Arg
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Ile Leu Ala Thr Arg His
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Gly Gln Glu Gly Phe Glu Ala Ser Ser Ala Pro Arg Asn Ile Pro Ser
            10                  15                  20

ggg gag ctg gac agc aac cct gac cct ggc acc ggc ccc agc cct gat      149
Gly Glu Leu Asp Ser Asn Pro Asp Pro Gly Thr Gly Pro Ser Pro Asp
        25                  30                  35

ggc ccc tca gac aca gag agc aag gaa ctg gga gta ccc aaa gac cct      197
Gly Pro Ser Asp Thr Glu Ser Lys Glu Leu Gly Val Pro Lys Asp Pro
    40                  45                  50

ctg ctc ttc att cag ctg aat gag ctg ctg ggc tgg ccc cag gcg ctg      245
Leu Leu Phe Ile Gln Leu Asn Glu Leu Leu Gly Trp Pro Gln Ala Leu
55                  60                  65                  70

gag tgg aga gag aca ggc agc tcc tct gca tct ctg ctc ctg gac atg      293
Glu Trp Arg Glu Thr Gly Ser Ser Ser Ala Ser Leu Leu Leu Asp Met
                75                  80                  85

gga gaa atg ccc tca ata aca ctg tct acc cac ctt cat cac agg tgg      341
Gly Glu Met Pro Ser Ile Thr Leu Ser Thr His Leu His His Arg Trp
            90                  95                  100

gta ctg ttt gag gag aag ttg gag gtg gct gca ggc cgg tgg agt gcc      389
Val Leu Phe Glu Glu Lys Leu Glu Val Ala Ala Gly Arg Trp Ser Ala
        105                 110                 115

ccc cac gtg ccc acc ctg gca ctg ccc agc ctc cag aag ctc cgc agc      437
Pro His Val Pro Thr Leu Ala Leu Pro Ser Leu Gln Lys Leu Arg Ser
    120                 125                 130

ctg ctg gcc gag ggc ctt gta ctg ctg gac tgc cca gct cag agc ctc      485
Leu Leu Ala Glu Gly Leu Val Leu Leu Asp Cys Pro Ala Gln Ser Leu
135                 140                 145                 150

ctg gag ctc gtg gag cag gtg acc agg gtg gag tcg ctg agc cca gag      533
Leu Glu Leu Val Glu Gln Val Thr Arg Val Glu Ser Leu Ser Pro Glu
                155                 160                 165

ctg aga ggg cag ttg cag gcc ttg ctg ctg cag aga ccc cag cat tac      581
Leu Arg Gly Gln Leu Gln Ala Leu Leu Leu Gln Arg Pro Gln His Tyr
            170                 175                 180

aac cag acc aca ggc acc agg ccc tgc tgg ggc tct act cat cca aga      629
Asn Gln Thr Thr Gly Thr Arg Pro Cys Trp Gly Ser Thr His Pro Arg
        185                 190                 195

aag gct tct gac aat gag gaa gcc ccc ctg agg gaa cag tgt cag aac      677
Lys Ala Ser Asp Asn Glu Glu Ala Pro Leu Arg Glu Gln Cys Gln Asn
    200                 205                 210

ccc ctg aga cag aag cta cct cca gga gct gag gca ggg act gtg ctg      725
Pro Leu Arg Gln Lys Leu Pro Pro Gly Ala Glu Ala Gly Thr Val Leu
215                 220                 225                 230

gca ggg gag ctg ggc ttc ctg gca cag cca ctg gga gcc ttt gtt cga      773
Ala Gly Glu Leu Gly Phe Leu Ala Gln Pro Leu Gly Ala Phe Val Arg
                235                 240                 245

ctg cgg aac cct gtg gta ctg ggg tcc ctt act gag gtg tcc ctc cca      821
Leu Arg Asn Pro Val Val Leu Gly Ser Leu Thr Glu Val Ser Leu Pro
            250                 255                 260

agc agg ttt ttc tgc ctt ctc ctg ggc ccc tgt atg ctg gga aag ggc      869
Ser Arg Phe Phe Cys Leu Leu Leu Gly Pro Cys Met Leu Gly Lys Gly
        265                 270                 275

tac cat gag atg gga cgg gca gca gct gtc ctc ctc agt gac ccg caa      917
Tyr His Glu Met Gly Arg Ala Ala Ala Val Leu Leu Ser Asp Pro Gln
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OCID: <WO_____03089583A2_I_>

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ttc cag tgg tca gtt cgt cgg gcc agc aac ctt cat gac ctt ctg gca      965
Phe Gln Trp Ser Val Arg Arg Ala Ser Asn Leu His Asp Leu Leu Ala
295                 300                 305                 310

gcc ctg gat gca ttc cta gag gag gtg aca gtg ctt ccc cca ggt cgg     1013
Ala Leu Asp Ala Phe Leu Glu Glu Val Thr Val Leu Pro Pro Gly Arg
                315                 320                 325

tgg gac cca aca gcc cgg att ccc ccg ccc aaa tgt ctg cca tct cag     1061
Trp Asp Pro Thr Ala Arg Ile Pro Pro Pro Lys Cys Leu Pro Ser Gln
            330                 335                 340

cac aaa agg ctt ccc tcg caa cag cgg gag atc aga ggt ccc gcc gtc     1109
His Lys Arg Leu Pro Ser Gln Gln Arg Glu Ile Arg Gly Pro Ala Val
        345                 350                 355

ccg cgc ctg acc tcg gct gag gac agg cac cgc cat ggg cca cac gca     1157
Pro Arg Leu Thr Ser Ala Glu Asp Arg His Arg His Gly Pro His Ala
    360                 365                 370

cac agc ccg gag ttg cag cgg acc ggc agg ctg ttt ggg ggc ctt atc     1205
His Ser Pro Glu Leu Gln Arg Thr Gly Arg Leu Phe Gly Gly Leu Ile
375                 380                 385                 390

cag gac gtg cgc agg aag gtc ccg tgg tac ccc agc gat ttc ttg gac     1253
Gln Asp Val Arg Arg Lys Val Pro Trp Tyr Pro Ser Asp Phe Leu Asp
                395                 400                 405

gcc ctg cat ctc cag tgc ttc tcg gcc gta ctc tac att tac ctg gcc     1301
Ala Leu His Leu Gln Cys Phe Ser Ala Val Leu Tyr Ile Tyr Leu Ala
            410                 415                 420

act gtc act aat gcc atc act ttt ggg ggt ctg ctg gga gat gcc act     1349
Thr Val Thr Asn Ala Ile Thr Phe Gly Gly Leu Leu Gly Asp Ala Thr
        425                 430                 435

gat ggt gcc cag gga gtg ctg gaa agt ttc ctg ggc aca gca gtg gct     1397
Asp Gly Ala Gln Gly Val Leu Glu Ser Phe Leu Gly Thr Ala Val Ala
    440                 445                 450

gga gct gcc ttc tgc ctg atg gca ggc cag ccc ctc acc att ctg agc     1445
Gly Ala Ala Phe Cys Leu Met Ala Gly Gln Pro Leu Thr Ile Leu Ser
455                 460                 465                 470

agc acg ggg cca gtg ctg gtc ttt gag cgc ctg ctc ttc tct ttc agc     1493
Ser Thr Gly Pro Val Leu Val Phe Glu Arg Leu Leu Phe Ser Phe Ser
                475                 480                 485

aga gat tac agc ctg gac tac ctg ccc ttc cgc cta tgg gtg ggc atc     1541
Arg Asp Tyr Ser Leu Asp Tyr Leu Pro Phe Arg Leu Trp Val Gly Ile
            490                 495                 500

tgg gtg gct acc ttt tgc ctg gtg ctg gtg gcc aca gag gcc agt gtg     1589
Trp Val Ala Thr Phe Cys Leu Val Leu Val Ala Thr Glu Ala Ser Val
        505                 510                 515

ctg gtg cgc tac ttc acc cgc ttc act gag gaa ggt ttc tgt gcc ctc     1637
Leu Val Arg Tyr Phe Thr Arg Phe Thr Glu Glu Gly Phe Cys Ala Leu
    520                 525                 530

atc agc ctc atc ttc atc tac gat gct gtg ggc aaa atg ctg aac ttg     1685
Ile Ser Leu Ile Phe Ile Tyr Asp Ala Val Gly Lys Met Leu Asn Leu
535                 540                 545                 550

acc cat acc tat cct atc cag aag cct ggg tcc tct gcc tac ggg tgc     1733
Thr His Thr Tyr Pro Ile Gln Lys Pro Gly Ser Ser Ala Tyr Gly Cys
                555                 560                 565

ctc tgc caa tac cca ggc cca gga gga aat gag tct caa tgg ata agg     1781
Leu Cys Gln Tyr Pro Gly Pro Gly Gly Asn Glu Ser Gln Trp Ile Arg
            570                 575                 580

aca agg cca aaa gac aga gac gac att gta agc atg gac tta ggc ctg     1829
Thr Arg Pro Lys Asp Arg Asp Asp Ile Val Ser Met Asp Leu Gly Leu
        585                 590                 595

atc aat gca tcc ttg ctg ccg cca cct gag tgc acc cgg cag gga ggc     1877
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Ile Asn Ala Ser Leu Leu Pro Pro Pro Glu Cys Thr Arg Gln Gly Gly
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cac cct cgt ggc cct ggc tgt cat aca gtc cca gac att gcc ttc ttc     1925
His Pro Arg Gly Pro Gly Cys His Thr Val Pro Asp Ile Ala Phe Phe
615                 620                 625                 630

tcc ctt ctc ctc ttc ctt act tct ttc ttc ttt gct atg gcc ctc aag     1973
Ser Leu Leu Leu Phe Leu Thr Ser Phe Phe Phe Ala Met Ala Leu Lys
                635                 640                 645

tgt gta aag acc agc cgc ttc ttc ccc tct gtg gtg cgc aaa ggg ctc     2021
Cys Val Lys Thr Ser Arg Phe Phe Pro Ser Val Val Arg Lys Gly Leu
            650                 655                 660

agc gac ttc tcc tca gtc ctg gcc atc ctg ctc ggc tgt ggc ctt gat     2069
Ser Asp Phe Ser Ser Val Leu Ala Ile Leu Leu Gly Cys Gly Leu Asp
        665                 670                 675

gct ttc ctg ggc cta gcc aca cca aag ctc atg gta ccc aga gag ttc     2117
Ala Phe Leu Gly Leu Ala Thr Pro Lys Leu Met Val Pro Arg Glu Phe
    680                 685                 690

aag ccc aca ctc cct ggg cgt ggc tgg ctg gtg tca cct ttt gga gcc     2165
Lys Pro Thr Leu Pro Gly Arg Gly Trp Leu Val Ser Pro Phe Gly Ala
695                 700                 705                 710

aac ccc tgg tgg tgg agt gtg gca gct gcc ctg cct gcc ctg ctg ctg     2213
Asn Pro Trp Trp Trp Ser Val Ala Ala Ala Leu Pro Ala Leu Leu Leu
                715                 720                 725

tct atc ctc atc ttc atg gac caa cag atc aca gca gtc atc ctc aac     2261
Ser Ile Leu Ile Phe Met Asp Gln Gln Ile Thr Ala Val Ile Leu Asn
            730                 735                 740

cgc atg gaa tac aga ctg cag aag gga gct ggc ttc cac ctg gac ctc     2309
Arg Met Glu Tyr Arg Leu Gln Lys Gly Ala Gly Phe His Leu Asp Leu
        745                 750                 755

ttc tgt gtg gct gtg ctg atg cta ctc aca tca gcg ctt gga ctg cct     2357
Phe Cys Val Ala Val Leu Met Leu Leu Thr Ser Ala Leu Gly Leu Pro
    760                 765                 770

tgg tat gtc tca gcc act gtc atc tcc ctg gct cac atg gac agt ctt     2405
Trp Tyr Val Ser Ala Thr Val Ile Ser Leu Ala His Met Asp Ser Leu
775                 780                 785                 790

cgg aga gag agc aga gcc tgt gcc ccc ggg gag cgc ccc aac ttc ctg     2453
Arg Arg Glu Ser Arg Ala Cys Ala Pro Gly Glu Arg Pro Asn Phe Leu
                795                 800                 805

ggt atc agg gaa cag agg ctg aca ggc ctg gtg gtg ttc atc ctt aca     2501
Gly Ile Arg Glu Gln Arg Leu Thr Gly Leu Val Val Phe Ile Leu Thr
            810                 815                 820

gga gcc tcc atc ttc ctg gca cct gtg ctc aag ttc att cca atg cct     2549
Gly Ala Ser Ile Phe Leu Ala Pro Val Leu Lys Phe Ile Pro Met Pro
        825                 830                 835

gtg ctc tat ggc atc ttc ctg tat atg ggg gtg gca gcg ctc agc agc     2597
Val Leu Tyr Gly Ile Phe Leu Tyr Met Gly Val Ala Ala Leu Ser Ser
    840                 845                 850

att cag ttc act aat agg gtg aag ctg ttg ttg atg cca gca aaa cac     2645
Ile Gln Phe Thr Asn Arg Val Lys Leu Leu Leu Met Pro Ala Lys His
855                 860                 865                 870

cag cca gac ctg cta ctc ttg cgg cat gtg cct ctg acc agg gtc cac     2693
Gln Pro Asp Leu Leu Leu Leu Arg His Val Pro Leu Thr Arg Val His
                875                 880                 885

ctc ttc aca gcc atc cag ctt gcc tgt ctg ggg ctg ctt tgg ata atc     2741
Leu Phe Thr Ala Ile Gln Leu Ala Cys Leu Gly Leu Leu Trp Ile Ile
            890                 895                 900

aag tct acc cct gca gcc atc atc ttc ccc ctc atg ttg ctg ggc ctt     2789
Lys Ser Thr Pro Ala Ala Ile Ile Phe Pro Leu Met Leu Leu Gly Leu
        905                 910                 915
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gtg ggg gtc cga aag gcc ctg gag agg gtc ttc tca cca cag gaa ctc      2837
Val Gly Val Arg Lys Ala Leu Glu Arg Val Phe Ser Pro Gln Glu Leu
    920                 925                 930

ctc tgg ctg gat gag ctg atg cca gag gag gag aga agc atc cct gag      2885
Leu Trp Leu Asp Glu Leu Met Pro Glu Glu Glu Arg Ser Ile Pro Glu
935                 940                 945                 950

aag ggg ctg gag cca gaa cac tca ttc agt gga agt gac agt gaa gat      2933
Lys Gly Leu Glu Pro Glu His Ser Phe Ser Gly Ser Asp Ser Glu Asp
                955                 960                 965

tca gag ctg atg tat cag cca aag gct cca gaa atc aac att tct gtg      2981
Ser Glu Leu Met Tyr Gln Pro Lys Ala Pro Glu Ile Asn Ile Ser Val
            970                 975                 980

aat tagctggagt aggagtctgg gagtggagac cccaggaaac agcatgaggt           3034
Asn


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            20                  25                  30


Thr Gly Pro Ser Pro Asp Gly Pro Ser Asp Thr Glu Ser Lys Glu Leu
        35                  40                  45


Gly Val Pro Lys Asp Pro Leu Leu Phe Ile Gln Leu Asn Glu Leu Leu
    50                  55                  60


Gly Trp Pro Gln Ala Leu Glu Trp Arg Glu Thr Gly Ser Ser Ser Ala
65                  70                  75                  80


Ser Leu Leu Leu Asp Met Gly Glu Met Pro Ser Ile Thr Leu Ser Thr
                85                  90                  95


His Leu His His Arg Trp Val Leu Phe Glu Glu Lys Leu Glu Val Ala
            100                 105                 110


Ala Gly Arg Trp Ser Ala Pro His Val Pro Thr Leu Ala Leu Pro Ser
        115                 120                 125


Leu Gln Lys Leu Arg Ser Leu Leu Ala Glu Gly Leu Val Leu Leu Asp
    130                 135                 140


Cys Pro Ala Gln Ser Leu Leu Glu Leu Val Glu Gln Val Thr Arg Val
145                 150                 155                 160


Glu Ser Leu Ser Pro Glu Leu Arg Gly Gln Leu Gln Ala Leu Leu Leu
                165                 170                 175


Gln Arg Pro Gln His Tyr Asn Gln Thr Thr Gly Thr Arg Pro Cys Trp
            180                 185                 190


Gly Ser Thr His Pro Arg Lys Ala Ser Asp Asn Glu Glu Ala Pro Leu
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195 200 205

Arg Glu Gln Cys Gln Asn Pro Leu Arg Gln Lys Leu Pro Pro Gly Ala
210 215 220

Glu Ala Gly Thr Val Leu Ala Gly Glu Leu Gly Phe Leu Ala Gln Pro
225 230 235 240

Leu Gly Ala Phe Val Arg Leu Arg Asn Pro Val Val Leu Gly Ser Leu
245 250 255

Thr Glu Val Ser Leu Pro Ser Arg Phe Phe Cys Leu Leu Leu Gly Pro
260 265 270

Cys Met Leu Gly Lys Gly Tyr His Glu Met Gly Arg Ala Ala Ala Val
275 280 285

Leu Leu Ser Asp Pro Gln Phe Gln Trp Ser Val Arg Arg Ala Ser Asn
290 295 300

Leu His Asp Leu Leu Ala Ala Leu Asp Ala Phe Leu Glu Glu Val Thr
305 310 315 320

Val Leu Pro Pro Gly Arg Trp Asp Pro Thr Ala Arg Ile Pro Pro Pro
325 330 335

Lys Cys Leu Pro Ser Gln His Lys Arg Leu Pro Ser Gln Gln Arg Glu
340 345 350

Ile Arg Gly Pro Ala Val Pro Arg Leu Thr Ser Ala Glu Asp Arg His
355 360 365

Arg His Gly Pro His Ala His Ser Pro Glu Leu Gln Arg Thr Gly Arg
370 375 380

Leu Phe Gly Gly Leu Ile Gln Asp Val Arg Arg Lys Val Pro Trp Tyr
385 390 395 400

Pro Ser Asp Phe Leu Asp Ala Leu His Leu Gln Cys Phe Ser Ala Val
405 410 415

Leu Tyr Ile Tyr Leu Ala Thr Val Thr Asn Ala Ile Thr Phe Gly Gly
420 425 430

Leu Leu Gly Asp Ala Thr Asp Gly Ala Gln Gly Val Leu Glu Ser Phe
435 440 445

Leu Gly Thr Ala Val Ala Gly Ala Ala Phe Cys Leu Met Ala Gly Gln
450 455 460

Pro Leu Thr Ile Leu Ser Ser Thr Gly Pro Val Leu Val Phe Glu Arg
465 470 475 480

Leu Leu Phe Ser Phe Ser Arg Asp Tyr Ser Leu Asp Tyr Leu Pro Phe
485 490 495

Arg Leu Trp Val Gly Ile Trp Val Ala Thr Phe Cys Leu Val Leu Val
500 505 510

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Ala Thr Glu Ala Ser Val Leu Val Arg Tyr Phe Thr Arg Phe Thr Glu
515 520 525

Glu Gly Phe Cys Ala Leu Ile Ser Leu Ile Phe Ile Tyr Asp Ala Val
530 535 540

Gly Lys Met Leu Asn Leu Thr His Thr Tyr Pro Ile Gln Lys Pro Gly
545 550 555 560

Ser Ser Ala Tyr Gly Cys Leu Cys Gln Tyr Pro Gly Pro Gly Gly Asn
565 570 575

Glu Ser Gln Trp Ile Arg Thr Arg Pro Lys Asp Arg Asp Asp Ile Val
580 585 590

Ser Met Asp Leu Gly Leu Ile Asn Ala Ser Leu Leu Pro Pro Pro Glu
595 600 605

Cys Thr Arg Gln Gly Gly His Pro Arg Gly Pro Gly Cys His Thr Val
610 615 620

Pro Asp Ile Ala Phe Phe Ser Leu Leu Leu Phe Leu Thr Ser Phe Phe
625 630 635 640

Phe Ala Met Ala Leu Lys Cys Val Lys Thr Ser Arg Phe Phe Pro Ser
645 650 655

Val Val Arg Lys Gly Leu Ser Asp Phe Ser Ser Val Leu Ala Ile Leu
660 665 670

Leu Gly Cys Gly Leu Asp Ala Phe Leu Gly Leu Ala Thr Pro Lys Leu
675 680 685

Met Val Pro Arg Glu Phe Lys Pro Thr Leu Pro Gly Arg Gly Trp Leu
690 695 700

Val Ser Pro Phe Gly Ala Asn Pro Trp Trp Trp Ser Val Ala Ala Ala
705 710 715 720

Leu Pro Ala Leu Leu Leu Ser Ile Leu Ile Phe Met Asp Gln Gln Ile
725 730 735

Thr Ala Val Ile Leu Asn Arg Met Glu Tyr Arg Leu Gln Lys Gly Ala
740 745 750

Gly Phe His Leu Asp Leu Phe Cys Val Ala Val Leu Met Leu Leu Thr
755 760 765

Ser Ala Leu Gly Leu Pro Trp Tyr Val Ser Ala Thr Val Ile Ser Leu
770 775 780

Ala His Met Asp Ser Leu Arg Arg Glu Ser Arg Ala Cys Ala Pro Gly
785 790 795 800

Glu Arg Pro Asn Phe Leu Gly Ile Arg Glu Gln Arg Leu Thr Gly Leu
805 810 815

Val Val Phe Ile Leu Thr Gly Ala Ser Ile Phe Leu Ala Pro Val Leu
820 825 830

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Lys Phe Ile Pro Met Pro Val Leu Tyr Gly Ile Phe Leu Tyr Met Gly
835 840 845

Val Ala Ala Leu Ser Ser Ile Gln Phe Thr Asn Arg Val Lys Leu Leu
850 855 860

Leu Met Pro Ala Lys His Gln Pro Asp Leu Leu Leu Leu Arg His Val
865 870 875 880

Pro Leu Thr Arg Val His Leu Phe Thr Ala Ile Gln Leu Ala Cys Leu
885 890 895

Gly Leu Leu Trp Ile Ile Lys Ser Thr Pro Ala Ala Ile Ile Phe Pro
900 905 910

Leu Met Leu Leu Gly Leu Val Gly Val Arg Lys Ala Leu Glu Arg Val
915 920 925

Phe Ser Pro Gln Glu Leu Leu Trp Leu Asp Glu Leu Met Pro Glu Glu
930 935 940

Glu Arg Ser Ile Pro Glu Lys Gly Leu Glu Pro Glu His Ser Phe Ser
945 950 955 960

Gly Ser Asp Ser Glu Asp Ser Glu Leu Met Tyr Gln Pro Lys Ala Pro
965 970 975

Glu Ile Asn Ile Ser Val Asn
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atg tca aga tcc aga ctt ttc agt gtc acc tca gcg atc tca acg ata 107
Met Ser Arg Ser Arg Leu Phe Ser Val Thr Ser Ala Ile Ser Thr Ile
1 5 10 15

ggg atc ttg tgt ttg ccg cta ttc cag ttg gtg ctc tcg gac cta cca 155
Gly Ile Leu Cys Leu Pro Leu Phe Gln Leu Val Leu Ser Asp Leu Pro
20 25 30

tgc gaa gaa gat gaa atg tgt gta aat tat aat gac caa cac cct aat 203
Cys Glu Glu Asp Glu Met Cys Val Asn Tyr Asn Asp Gln His Pro Asn
35 40 45

ggc tgg tat atc tgg atc ctc ctg ctg ctg gtt ttg gtg gca gct ctt 251
Gly Trp Tyr Ile Trp Ile Leu Leu Leu Leu Val Leu Val Ala Ala Leu
50 55 60

ctc tgt gga gct gtg gtc ctc tgc ctc cag tgc tgg ctg agg aga ccc 299
Leu Cys Gly Ala Val Val Leu Cys Leu Gln Cys Trp Leu Arg Arg Pro
65 70 75 80

cga att gat tct cac agg cgc acc atg gca gtt ttt gct gtt gga gac 347
Arg Ile Asp Ser His Arg Arg Thr Met Ala Val Phe Ala Val Gly Asp
85 90 95

ttg gac tct att tat ggg aca gaa gca gct gtg agt cca act gtt gga 395

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Ile His Leu Gln Thr Gln Thr Pro Asp Leu Tyr Pro Val Pro Ala Pro
        115                 120                 125

tgt ttt ggc cct tta ggc tcc cca cct cca tat gaa gaa att gta aaa      491
Cys Phe Gly Pro Leu Gly Ser Pro Pro Pro Tyr Glu Glu Ile Val Lys
    130                 135                 140

aca acc tgattttagg tgtggattat caatttaaag tattaacgac atctgtaatt      547
Thr Thr
145

ccaaaacatc aaatttagga atagttattt cagttgttgg aaatgtccag agatctattc    607

atatagtctg aggaaggaca attcgacaaa agaatggatg ttggaaaaaa ttttggtcat    667

ggagatgttt aaatagtaaa gtagcaggct ttt                                 700


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1               5                   10                  15


Gly Ile Leu Cys Leu Pro Leu Phe Gln Leu Val Leu Ser Asp Leu Pro
            20                  25                  30


Cys Glu Glu Asp Glu Met Cys Val Asn Tyr Asn Asp Gln His Pro Asn
        35                  40                  45


Gly Trp Tyr Ile Trp Ile Leu Leu Leu Leu Val Leu Val Ala Ala Leu
    50                  55                  60


Leu Cys Gly Ala Val Val Leu Cys Leu Gln Cys Trp Leu Arg Arg Pro
65                  70                  75                  80


Arg Ile Asp Ser His Arg Arg Thr Met Ala Val Phe Ala Val Gly Asp
                85                  90                  95


Leu Asp Ser Ile Tyr Gly Thr Glu Ala Ala Val Ser Pro Thr Val Gly
            100                 105                 110


Ile His Leu Gln Thr Gln Thr Pro Asp Leu Tyr Pro Val Pro Ala Pro
        115                 120                 125


Cys Phe Gly Pro Leu Gly Ser Pro Pro Pro Tyr Glu Glu Ile Val Lys
    130                 135                 140


Thr Thr
145


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                                                1

agc ggc cgc ttg gag gac ttc cct gtc aat gtg ttc tcc gtc act cct      103
Ser Gly Arg Leu Glu Asp Phe Pro Val Asn Val Phe Ser Val Thr Pro
5                   10                  15                  20

tac aca ccc agc acc gct gac atc cag gtg tcc gat gat gac aag gcg      151
Tyr Thr Pro Ser Thr Ala Asp Ile Gln Val Ser Asp Asp Asp Lys Ala
                25                  30                  35

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Gly Ala Thr Leu Leu Phe Ser Gly Ile Phe Leu Gly Leu Val Gly Ile
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aca ttc act gtc atg ggc tgg atc aaa tac caa ggt gtc tcc cac ttt      247
Thr Phe Thr Val Met Gly Trp Ile Lys Tyr Gln Gly Val Ser His Phe
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gaa tgg acc cag ctc ctt ggg ccc gtc ctg ctg tca gtt ggg gtg aca      295
Glu Trp Thr Gln Leu Leu Gly Pro Val Leu Leu Ser Val Gly Val Thr
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Phe Ile Leu Ile Ala Val Cys Lys Phe Lys Met Leu Ser Cys Gln Leu
85                  90                  95                  100

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Cys Lys Glu Ser Glu Glu Arg Val Pro Asp Ser Glu Gln Thr Pro Gly
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Gly Pro Ser Phe Val Phe Thr Gly Ile Asn Gln Pro Ile Thr Phe His
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Gly Ala Thr Val Val Gln Tyr Ile Pro Pro Pro Tyr Gly Ser Pro Glu
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cct atg ggg ata aat acc agc tac ctg cag tct gtg gtg agc ccc tgc      535
Pro Met Gly Ile Asn Thr Ser Tyr Leu Gln Ser Val Val Ser Pro Cys
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ggc ctc ata acc tct gga ggg gca gca gcc gcc atg tca agt cct cct      583
Gly Leu Ile Thr Ser Gly Gly Ala Ala Ala Ala Met Ser Ser Pro Pro
165                 170                 175                 180

caa tac tac acc atc tac cct caa gat aac tct gca ttt gtg gtt gat      631
Gln Tyr Tyr Thr Ile Tyr Pro Gln Asp Asn Ser Ala Phe Val Val Asp
                185                 190                 195

gag ggc tgc ctt tct ttc acg gac ggt gga aat cac agg ccc aat cct      679
Glu Gly Cys Leu Ser Phe Thr Asp Gly Gly Asn His Arg Pro Asn Pro
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gat gtt gac cag cta gaa gag aca cag ctg gaa gag gag gcc tgt gcc      727
Asp Val Asp Gln Leu Glu Glu Thr Gln Leu Glu Glu Glu Ala Cys Ala
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tgc ttc tct cct ccc cct tat gaa gaa ata tac tct ctc cct cgc          772
Cys Phe Ser Pro Pro Pro Tyr Glu Glu Ile Tyr Ser Leu Pro Arg
    230                 235                 240

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gcagcctgac agagatcatt caaggggga aaggggaagt gggaggtgca atttctcaga   952

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35 40 45

Leu Val Gly Ile Thr Phe Thr Val Met Gly Trp Ile Lys Tyr Gln Gly
50 55 60

Val Ser His Phe Glu Trp Thr Gln Leu Leu Gly Pro Val Leu Leu Ser
65 70 75 80

Val Gly Val Thr Phe Ile Leu Ile Ala Val Cys Lys Phe Lys Met Leu
85 90 95

Ser Cys Gln Leu Cys Lys Glu Ser Glu Glu Arg Val Pro Asp Ser Glu
100 105 110

Gln Thr Pro Gly Gly Pro Ser Phe Val Phe Thr Gly Ile Asn Gln Pro
115 120 125

Ile Thr Phe His Gly Ala Thr Val Val Gln Tyr Ile Pro Pro Pro Tyr
130 135 140

Gly Ser Pro Glu Pro Met Gly Ile Asn Thr Ser Tyr Leu Gln Ser Val
145 150 155 160

Val Ser Pro Cys Gly Leu Ile Thr Ser Gly Gly Ala Ala Ala Ala Met
165 170 175

Ser Ser Pro Pro Gln Tyr Tyr Thr Ile Tyr Pro Gln Asp Asn Ser Ala
180 185 190

Phe Val Val Asp Glu Gly Cys Leu Ser Phe Thr Asp Gly Gly Asn His
195 200 205

Arg Pro Asn Pro Asp Val Asp Gln Leu Glu Glu Thr Gln Leu Glu Glu
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Glu Ala Cys Ala Cys Phe Ser Pro Pro Pro Tyr Glu Glu Ile Tyr Ser
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gctttctgag ttcttggata tctgagagac agggcctcta tgctgtttca ctgctggata 180

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gcatccatat gtaaatcaca gaattctgaa caagagaaag atagtgctat caacgggaaa 900

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cgg ctg gcc aac cag acc ctg ggt ggt gac ttt ttc ctg ttg gga atc      2325
Arg Leu Ala Asn Gln Thr Leu Gly Gly Asp Phe Phe Leu Leu Gly Ile
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ttc agc cag atc tca cac cct ggc cgc ctc tgc ttg ctt atc ttc agt      2373
Phe Ser Gln Ile Ser His Pro Gly Arg Leu Cys Leu Leu Ile Phe Ser
          20                  25                  30

ata ttt ttg atg gct gtg tct tgg aat att aca ttg ata ctt ctg atc      2421
Ile Phe Leu Met Ala Val Ser Trp Asn Ile Thr Leu Ile Leu Leu Ile
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cac att gac tcc tct ctg cat act ccc atg tac ttc ttt ata aac cag      2469
His Ile Asp Ser Ser Leu His Thr Pro Met Tyr Phe Phe Ile Asn Gln
  50                  55                  60                  65

ctc tca ctc ata gac ttg aca tat att tct gtc act gtc ccc aaa atg      2517
Leu Ser Leu Ile Asp Leu Thr Tyr Ile Ser Val Thr Val Pro Lys Met
                  70                  75                  80

ctg gtg aac cag ctg gcc aaa gac aag acc atc tcg gtc ctt ggg tgt      2565
Leu Val Asn Gln Leu Ala Lys Asp Lys Thr Ile Ser Val Leu Gly Cys
              85                  90                  95

ggc acc cag atg tac ttc tac ctg cag ttg gga ggt gca gag tgc tgc      2613
Gly Thr Gln Met Tyr Phe Tyr Leu Gln Leu Gly Gly Ala Glu Cys Cys
          100                 105                 110

ctt cta gcc gcc atg gcc tat gac cgc tat gtg gct atc tgc cat cct      2661
Leu Leu Ala Ala Met Ala Tyr Asp Arg Tyr Val Ala Ile Cys His Pro
      115                 120                 125

ctc cgt tac tct gtg ctc atg agc cat agg gta tgt ctc ctc ctg gca      2709
Leu Arg Tyr Ser Val Leu Met Ser His Arg Val Cys Leu Leu Leu Ala
  130                 135                 140                 145

tca ggc tgc tgg ttt gtg ggc tca gtg gat ggc ttc atg ctc act ccc      2757
Ser Gly Cys Trp Phe Val Gly Ser Val Asp Gly Phe Met Leu Thr Pro
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atc gcc atg agc ttc ccc ttc tgc aga tcc cat gag att cag cac ttc      2805
Ile Ala Met Ser Phe Pro Phe Cys Arg Ser His Glu Ile Gln His Phe
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ttc tgt gag gtc cct gct gtt ttg aag ctc tct tgc tca gac acc tca      2853
Phe Cys Glu Val Pro Ala Val Leu Lys Leu Ser Cys Ser Asp Thr Ser
          180                 185                 190

ctt tac aag att ttc atg tac ttg tgc tgt gtc atc atg ctc ctg ata      2901
Leu Tyr Lys Ile Phe Met Tyr Leu Cys Cys Val Ile Met Leu Leu Ile
      195                 200                 205

cct gtg acg gtc att tca gtg tct tac tac tat atc atc etc acc atc      2949
Pro Val Thr Val Ile Ser Val Ser Tyr Tyr Tyr Ile Ile Leu Thr Ile
  210                 215                 220                 225

cat aag atg aac tca gtt gag ggt cgg aaa aag gcc ttc acc acc tgc      2997
His Lys Met Asn Ser Val Glu Gly Arg Lys Lys Ala Phe Thr Thr Cys
                  230                 235                 240

tcc tcc cac att aca gtg gtc agc ctc ttc tat gga gct gct att tac      3045
Ser Ser His Ile Thr Val Val Ser Leu Phe Tyr Gly Ala Ala Ile Tyr
              245                 250                 255

aac tac atg ctc ccc agc tcc tac caa act cct gag aaa gat atg atg      3093
Asn Tyr Met Leu Pro Ser Ser Tyr Gln Thr Pro Glu Lys Asp Met Met
          260                 265                 270

tca tcc ttt ttc tac act atc ctt aca cct gtc ttg aat cct atc att      3141
Ser Ser Phe Phe Tyr Thr Ile Leu Thr Pro Val Leu Asn Pro Ile Ile
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agc gtg cag aaa cct cca tat taa agtgtgaaag aacttaagtt ggtcctctct 3243
Ser Val Gln Lys Pro Pro Tyr
310

tcttagagtc tctcttcact ttaggtgtcc ttccaccaaa caatcagcat attgtggtag 3303

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Ser Ile Phe Leu Met Ala Val Ser Trp Asn Ile Thr Leu Ile Leu Leu
35 40 45

Ile His Ile Asp Ser Ser Leu His Thr Pro Met Tyr Phe Phe Ile Asn
50 55 60

Gln Leu Ser Leu Ile Asp Leu Thr Tyr Ile Ser Val Thr Val Pro Lys
65 70 75 80

Met Leu Val Asn Gln Leu Ala Lys Asp Lys Thr Ile Ser Val Leu Gly
85 90 95

Cys Gly Thr Gln Met Tyr Phe Tyr Leu Gln Leu Gly Gly Ala Glu Cys
100 105 110

Cys Leu Leu Ala Ala Met Ala Tyr Asp Arg Tyr Val Ala Ile Cys His
115 120 125

Pro Leu Arg Tyr Ser Val Leu Met Ser His Arg Val Cys Leu Leu Leu
130 135 140

Ala Ser Gly Cys Trp Phe Val Gly Ser Val Asp Gly Phe Met Leu Thr
145 150 155 160

Pro Ile Ala Met Ser Phe Pro Phe Cys Arg Ser His Glu Ile Gln His
165 170 175

Phe Phe Cys Glu Val Pro Ala Val Leu Lys Leu Ser Cys Ser Asp Thr
180 185 190

Ser Leu Tyr Lys Ile Phe Met Tyr Leu Cys Cys Val Ile Met Leu Leu
195 200 205

Ile Pro Val Thr Val Ile Ser Val Ser Tyr Tyr Tyr Ile Ile Leu Thr
210 215 220

Ile His Lys Met Asn Ser Val Glu Gly Arg Lys Lys Ala Phe Thr Thr
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Cys Ser Ser His Ile Thr Val Val Ser Leu Phe Tyr Gly Ala Ala Ile
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Tyr Asn Tyr Met Leu Pro Ser Ser Tyr Gln Thr Pro Glu Lys Asp Met
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Leu Gln Pro Leu Lys Thr Cys Pro Val Ala Arg Gln Leu Ile Arg Gly
            20                  25                  30

gtg ctg cgg gca cct gat gga gcc aag cca gga gag gac agg ggc cag     144
Val Leu Arg Ala Pro Asp Gly Ala Lys Pro Gly Glu Asp Arg Gly Gln
        35                  40                  45

gcc cgc tgc aat gga cgt gta tgt gga gag aaa tca aaa caa cct att     192
Ala Arg Cys Asn Gly Arg Val Cys Gly Glu Lys Ser Lys Gln Pro Ile
    50                  55                  60

gag gct ttt aag ccc gtc tgc tac aaa ccc caa ttt atg tcc cac att     240
Glu Ala Phe Lys Pro Val Cys Tyr Lys Pro Gln Phe Met Ser His Ile
65                  70                  75                  80

att ccc ctt tac tcc atc cat gca tcc cag agt tcc agc caa tcc aag     288
Ile Pro Leu Tyr Ser Ile His Ala Ser Gln Ser Ser Ser Gln Ser Lys
                85                  90                  95

ctg cct gca cat ctc cat ttg gac ccc tta ggc tgt gcc agt ctc agc     336
Leu Pro Ala His Leu His Leu Asp Pro Leu Gly Cys Ala Ser Leu Ser
            100                 105                 110

ttc tcc tcc acc cag ccc tca cca cct tat tac cca ggg ttg gta cta     384
Phe Ser Ser Thr Gln Pro Ser Pro Pro Tyr Tyr Pro Gly Leu Val Leu
        115                 120                 125

gga tgc agc aag cag aat act gga ggt gca aaa tgt cag aag cca ctc     432
Gly Cys Ser Lys Gln Asn Thr Gly Gly Ala Lys Cys Gln Lys Pro Leu
    130                 135                 140

act cgc agg ttt gag cac ttg gga aca gca aag aag ccc aag aaa tca     480
Thr Arg Arg Phe Glu His Leu Gly Thr Ala Lys Lys Pro Lys Lys Ser
145                 150                 155                 160

gtc tgg cca ctg cag agc ctg cct caa aga gat ttg aag ctg gtc aat     528
Val Trp Pro Leu Gln Ser Leu Pro Gln Arg Asp Leu Lys Leu Val Asn
                165                 170                 175

gca agg agc cag gcc tgc tgg aat cca agg acc tgg ggt gca gca acc     576
Ala Arg Ser Gln Ala Cys Trp Asn Pro Arg Thr Trp Gly Ala Ala Thr
            180                 185                 190

cca gat aca gac cct gaa gag gcc aac agc ggt cag cag aac ata aag     624
Pro Asp Thr Asp Pro Glu Glu Ala Asn Ser Gly Gln Gln Asn Ile Lys
        195                 200                 205

gag caa cag tac cgt gtc tct ctg ggg aac aac act ggt tct ccc ttg     672
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225                 230                 235                 240

aga acc acc agg gaa gca tgg aag gag gcc agc cgc tgg gat ctg cca      768
Arg Thr Thr Arg Glu Ala Trp Lys Glu Ala Ser Arg Trp Asp Leu Pro
                245                 250                 255

gct ctg ggc ccc agc ggc cac cct ctg cag ctc aaa gtc acc ttt gct      816
Ala Leu Gly Pro Ser Gly His Pro Leu Gln Leu Lys Val Thr Phe Ala
            260                 265                 270

cct ctc ctc tcc tcg gct ggc cag cca gaa cca gcc cag aac tcc ctc      864
Pro Leu Leu Ser Ser Ala Gly Gln Pro Glu Pro Ala Gln Asn Ser Leu
        275                 280                 285

ccc tcc gct cag cag gac cca gga act ggt ccc tac tgg gca att att      912
Pro Ser Ala Gln Gln Asp Pro Gly Thr Gly Pro Tyr Trp Ala Ile Ile
    290                 295                 300

aat cag att ctt gac att cct cag ccc cag gtt ggc tgg aga agc atg      960
Asn Gln Ile Leu Asp Ile Pro Gln Pro Gln Val Gly Trp Arg Ser Met
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ttc ccc aga gga gca gag gcc cag gac tgg cat ttg gat atg cag ctg     1008
Phe Pro Arg Gly Ala Glu Ala Gln Asp Trp His Leu Asp Met Gln Leu
                325                 330                 335

acc ggc aag gtg gtg ctg tca gcc gct gcc ctg ctc ctg gtg act gtg     1056
Thr Gly Lys Val Val Leu Ser Ala Ala Ala Leu Leu Leu Val Thr Val
            340                 345                 350

gcc tac agg ctg tac aag tcg agg cct gcc cca gcc cag cgg tgg ggt     1104
Ala Tyr Arg Leu Tyr Lys Ser Arg Pro Ala Pro Ala Gln Arg Trp Gly
        355                 360                 365

ggg aat ggc cag gca gaa gcc aag gag gaa gca gag ggc tca ggg cag     1152
Gly Asn Gly Gln Ala Glu Ala Lys Glu Glu Ala Glu Gly Ser Gly Gln
    370                 375                 380

cct gct gta cag gag gct tct cct ggg gtg ctc ctg agg ggg cca aga     1200
Pro Ala Val Gln Glu Ala Ser Pro Gly Val Leu Leu Arg Gly Pro Arg
385                 390                 395                 400

cgt cgg agg agc agc aag cgg gct gaa gca cca cag ggc tgc agc tgt     1248
Arg Arg Arg Ser Ser Lys Arg Ala Glu Ala Pro Gln Gly Cys Ser Cys
                405                 410                 415

gag aat cca aga ggc ccc tat gtc ctg gtc acg ggg gcc act tcc aca     1296
Glu Asn Pro Arg Gly Pro Tyr Val Leu Val Thr Gly Ala Thr Ser Thr
            420                 425                 430

gac agg aag ccc cag aga aaa ggc tca ggt gag gag cgg ggc ggg cag     1344
Asp Arg Lys Pro Gln Arg Lys Gly Ser Gly Glu Glu Arg Gly Gly Gln
        435                 440                 445

ggc tcg gac tct gag cag gtg cct cct tgc tgc ccc agc cag gaa acc     1392
Gly Ser Asp Ser Glu Gln Val Pro Pro Cys Cys Pro Ser Gln Glu Thr
    450                 455                 460

aga aca gct gtt ggc agt aac cct gac cct ccc cat ttc ccc cgc ttg     1440
Arg Thr Ala Val Gly Ser Asn Pro Asp Pro Pro His Phe Pro Arg Leu
465                 470                 475                 480

ggc agc gaa ccg aag agc tcc cca gct gga ctc att gca gca gcc gac     1488
Gly Ser Glu Pro Lys Ser Ser Pro Ala Gly Leu Ile Ala Ala Ala Asp
                485                 490                 495

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Gly Ser Cys Ala Gly Gly Glu Pro Ser Pro Trp Gln Asp Ser Lys Pro
            500                 505                 510

cgt gag cat cca gga ctg ggg caa cta gaa cct ccc cac tgt cac tac     1584
Arg Glu His Pro Gly Leu Gly Gln Leu Glu Pro Pro His Cys His Tyr
        515                 520                 525

gtg gct ccc ttg caa ggc agc agt gac atg aac cag agc tgg gtc ttc     1632
Val Ala Pro Leu Gln Gly Ser Ser Asp Met Asn Gln Ser Trp Val Phe
    530                 535                 540
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acc cgt gtg ata ggg gtc agc aga gaa gag gct ggg gct ctc gag gct      1680
Thr Arg Val Ile Gly Val Ser Arg Glu Glu Ala Gly Ala Leu Glu Ala
545                 550                 555                 560

gcc tcc gat gtt gac ctg acc ctg cat cag cag gag ggc gcc ccc aac      1728
Ala Ser Asp Val Asp Leu Thr Leu His Gln Gln Glu Gly Ala Pro Asn
                565                 570                 575

tcc tcc tat acc ttc tca tcc ata gcc cgc gtc cga atg gag gag cat      1776
Ser Ser Tyr Thr Phe Ser Ser Ile Ala Arg Val Arg Met Glu Glu His
            580                 585                 590

ttc ata cag aag gcg gag ggg gtt gag ccc cgg ctc aag ggc aag gtg      1824
Phe Ile Gln Lys Ala Glu Gly Val Glu Pro Arg Leu Lys Gly Lys Val
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tac gac tac tat gtg gaa tct acc tct cag gcc atc ttc cag ggc agg      1872
Tyr Asp Tyr Tyr Val Glu Ser Thr Ser Gln Ala Ile Phe Gln Gly Arg
    610                 615                 620

ctg gct ccc agg aca gca gcc ctg act gag gtt cca tcc cct agg cca      1920
Leu Ala Pro Arg Thr Ala Ala Leu Thr Glu Val Pro Ser Pro Arg Pro
625                 630                 635                 640

ccg cca ggg tcc ctg gga aca ggg gct gcc tcg gga ggc caa gcc ggt      1968
Pro Pro Gly Ser Leu Gly Thr Gly Ala Ala Ser Gly Gly Gln Ala Gly
                645                 650                 655

gac aca aag ggt gca gcc gaa aga gcc gcc tcc ccg cag aca ggg ccg      2016
Asp Thr Lys Gly Ala Ala Glu Arg Ala Ala Ser Pro Gln Thr Gly Pro
            660                 665                 670

tgg ccc tcc acc cga ggc ttc agc cgg aag gag agc ctt ctg cag ata      2064
Trp Pro Ser Thr Arg Gly Phe Ser Arg Lys Glu Ser Leu Leu Gln Ile
        675                 680                 685

gcg gag aac cca gag ctg cag ctg cag cca gat ggc ttc cgg ctc ccc      2112
Ala Glu Asn Pro Glu Leu Gln Leu Gln Pro Asp Gly Phe Arg Leu Pro
    690                 695                 700

gct cca ccc tgc cca gac ccg ggc gcc ctg cct ggc tta ggc aga agc      2160
Ala Pro Pro Cys Pro Asp Pro Gly Ala Leu Pro Gly Leu Gly Arg Ser
705                 710                 715                 720

agc cgg gag ccc cat gtg cag ccg gtg gcc ggg acc aat ttc ttc cat      2208
Ser Arg Glu Pro His Val Gln Pro Val Ala Gly Thr Asn Phe Phe His
                725                 730                 735

atc ccg ctc acc cct gct tca gcc cca cag gtc cgc ctg gat ctg ggc      2256
Ile Pro Leu Thr Pro Ala Ser Ala Pro Gln Val Arg Leu Asp Leu Gly
            740                 745                 750

aat tgc tat gag gtg ctg acc ttg gcc aag agg cag aac ctg gag gcc      2304
Asn Cys Tyr Glu Val Leu Thr Leu Ala Lys Arg Gln Asn Leu Glu Ala
        755                 760                 765

ctg aaa gag gcg gcc tac aag gtg atg agc gaa aac tac ctg cag gtg      2352
Leu Lys Glu Ala Ala Tyr Lys Val Met Ser Glu Asn Tyr Leu Gln Val
    770                 775                 780

ctg cgc agc ccg gac atc tac ggg tgc ctg agc ggg gca gag cgc gag      2400
Leu Arg Ser Pro Asp Ile Tyr Gly Cys Leu Ser Gly Ala Glu Arg Glu
785                 790                 795                 800

ctg atc ctg cag cgc cgg ctc cgg ggc cgc cag tac ctg gtg gtg gct      2448
Leu Ile Leu Gln Arg Arg Leu Arg Gly Arg Gln Tyr Leu Val Val Ala
                805                 810                 815

gac gtg tgc ccc aag gaa gac tcc ggc ggc ctc tgt tgc tat gac gat      2496
Asp Val Cys Pro Lys Glu Asp Ser Gly Gly Leu Cys Cys Tyr Asp Asp
            820                 825                 830

gag cag gat gtc tgg cgc ccg ctg gct cgc atg ccc ccc gag gcc gtg      2544
Glu Gln Asp Val Trp Arg Pro Leu Ala Arg Met Pro Pro Glu Ala Val
        835                 840                 845

tcc cgg ggc tgt gcc atc tgc agt ctc ttc aat tat ctc ttc gtg gtg      2592
Ser Arg Gly Cys Ala Ile Cys Ser Leu Phe Asn Tyr Leu Phe Val Val
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tcc ggc tgc cag ggg ccc ggg cac cag ccc tcc agc cgc gtc ttc tgc     2640
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865                 870                 875                 880

tac aac ccg ctc acg ggg atc tgg agc gag gtg tgc ccg ctg aac cag     2688
Tyr Asn Pro Leu Thr Gly Ile Trp Ser Glu Val Cys Pro Leu Asn Gln
                885                 890                 895

gcc cgg ccg cac tgc cgg ctg gtg gcc ctg gac ggg cac ctg tat gcc     2736
Ala Arg Pro His Cys Arg Leu Val Ala Leu Asp Gly His Leu Tyr Ala
            900                 905                 910

atc ggc gga gag tgt ctg aac tcg gtg gag cgt tac gac ccc cgc ctg     2784
Ile Gly Gly Glu Cys Leu Asn Ser Val Glu Arg Tyr Asp Pro Arg Leu
        915                 920                 925

gac cgc tgg gac ttt gcc ccg ccg ctc ccc agt gac acg ttc gcc ctg     2832
Asp Arg Trp Asp Phe Ala Pro Pro Leu Pro Ser Asp Thr Phe Ala Leu
    930                 935                 940

gcg cac acg gcc acg gtg cgt gcc aag gaa atc ttc gtc acc ggc ggc     2880
Ala His Thr Ala Thr Val Arg Ala Lys Glu Ile Phe Val Thr Gly Gly
945                 950                 955                 960

tcg ctg cgc ttc ctg ctg ttc cgc ttc tct gcg cag gag cag cgc tgg     2928
Ser Leu Arg Phe Leu Leu Phe Arg Phe Ser Ala Gln Glu Gln Arg Trp
                965                 970                 975

tgg gcc ggc ccc acc ggg ggc agc aag gac cgc acg gcc gag atg gtg     2976
Trp Ala Gly Pro Thr Gly Gly Ser Lys Asp Arg Thr Ala Glu Met Val
            980                 985                 990

gcg gtc aac ggc ttt ctc tac cgc  ttt gac ctc aac cgc  agc ctg ggc   3024
Ala Val Asn Gly Phe Leu Tyr Arg  Phe Asp Leu Asn Arg  Ser Leu Gly
        995                 1000                1005

atc gcc  gtg tac cgc tgc agc  gcc agc acc cgg ctc  tgg tac gag      3069
Ile Ala  Val Tyr Arg Cys Ser  Ala Ser Thr Arg Leu  Trp Tyr Glu
    1010                1015                1020

tgc gcc  acg tac cgg acg cct  tac ccg gat gcc ttc  cag tgc gcc      3114
Cys Ala  Thr Tyr Arg Thr Pro  Tyr Pro Asp Ala Phe  Gln Cys Ala
    1025                1030                1035

gtg gtg  gac aac ctc atc tac  tgc gtg gga cgc cgg  agc acc ctc      3159
Val Val  Asp Asn Leu Ile Tyr  Cys Val Gly Arg Arg  Ser Thr Leu
    1040                1045                1050

tgc ttc  cta gca gac tct gtc  tca ccc aga tct gta  gcc gtc ttc      3204
Cys Phe  Leu Ala Asp Ser Val  Ser Pro Arg Ser Val  Ala Val Phe
    1055                1060                1065

ctg tct  gga agc tgg ggc aac  cac cac cag tca gca  ctt cag ggt      3249
Leu Ser  Gly Ser Trp Gly Asn  His His Gln Ser Ala  Leu Gln Gly
    1070                1075                1080

gac agc  ata att tgc cct cct  tgt gcc agg tgg tcc  cag cta gat      3294
Asp Ser  Ile Ile Cys Pro Pro  Cys Ala Arg Trp Ser  Gln Leu Asp
    1085                1090                1095

cct gtg  tcc acg gaa gct gct  ggt gcc cag gct gtg  ggt ctt gtt      3339
Pro Val  Ser Thr Glu Ala Ala  Gly Ala Gln Ala Val  Gly Leu Val
    1100                1105                1110

gga aga  agc agg act gga aca  aag gat gaa aag gag  gtt ggc atg      3384
Gly Arg  Ser Arg Thr Gly Thr  Lys Asp Glu Lys Glu  Val Gly Met
    1115                1120                1125

gac ata  aga gga gag ctt gca  ctg gac cac cga aga  cca cca tcc      3429
Asp Ile  Arg Gly Glu Leu Ala  Leu Asp His Arg Arg  Pro Pro Ser
    1130                1135                1140

ctg gtc  tgg gct ctg gca cca  ggc tct gcc agt ggc  agc tca gag      3474
Leu Val  Trp Ala Leu Ala Pro  Gly Ser Ala Ser Gly  Ser Ser Glu
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gcc aca  ggg tga                                                 3486
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35 40 45

Ala Arg Cys Asn Gly Arg Val Cys Gly Glu Lys Ser Lys Gln Pro Ile
50 55 60

Glu Ala Phe Lys Pro Val Cys Tyr Lys Pro Gln Phe Met Ser His Ile
65 70 75 80

Ile Pro Leu Tyr Ser Ile His Ala Ser Gln Ser Ser Ser Gln Ser Lys
85 90 95

Leu Pro Ala His Leu His Leu Asp Pro Leu Gly Cys Ala Ser Leu Ser
100 105 110

Phe Ser Ser Thr Gln Pro Ser Pro Pro Tyr Tyr Pro Gly Leu Val Leu
115 120 125

Gly Cys Ser Lys Gln Asn Thr Gly Gly Ala Lys Cys Gln Lys Pro Leu
130 135 140

Thr Arg Arg Phe Glu His Leu Gly Thr Ala Lys Lys Pro Lys Lys Ser
145 150 155 160

Val Trp Pro Leu Gln Ser Leu Pro Gln Arg Asp Leu Lys Leu Val Asn
165 170 175

Ala Arg Ser Gln Ala Cys Trp Asn Pro Arg Thr Trp Gly Ala Ala Thr
180 185 190

Pro Asp Thr Asp Pro Glu Glu Ala Asn Ser Gly Gln Gln Asn Ile Lys
195 200 205

Glu Gln Gln Tyr Arg Val Ser Leu Gly Asn Asn Thr Gly Ser Pro Leu
210 215 220

Cys Ser Thr Glu Val Asn Phe Gly Ser Arg Gln Gln Gly Lys Leu Asn
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Ala Leu Gly Pro Ser Gly His Pro Leu Gln Leu Lys Val Thr Phe Ala
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290 295 300

Asn Gln Ile Leu Asp Ile Pro Gln Pro Gln Val Gly Trp Arg Ser Met
305 310 315 320

Phe Pro Arg Gly Ala Glu Ala Gln Asp Trp His Leu Asp Met Gln Leu
325 330 335

Thr Gly Lys Val Val Leu Ser Ala Ala Ala Leu Leu Leu Val Thr Val
340 345 350

Ala Tyr Arg Leu Tyr Lys Ser Arg Pro Ala Pro Ala Gln Arg Trp Gly
355 360 365

Gly Asn Gly Gln Ala Glu Ala Lys Glu Glu Ala Glu Gly Ser Gly Gln
370 375 380

Pro Ala Val Gln Glu Ala Ser Pro Gly Val Leu Leu Arg Gly Pro Arg
385 390 395 400

Arg Arg Arg Ser Ser Lys Arg Ala Glu Ala Pro Gln Gly Cys Ser Cys
405 410 415

Glu Asn Pro Arg Gly Pro Tyr Val Leu Val Thr Gly Ala Thr Ser Thr
420 425 430

Asp Arg Lys Pro Gln Arg Lys Gly Ser Gly Glu Glu Arg Gly Gly Gln
435 440 445

Gly Ser Asp Ser Glu Gln Val Pro Pro Cys Cys Pro Ser Gln Glu Thr
450 455 460

Arg Thr Ala Val Gly Ser Asn Pro Asp Pro Pro His Phe Pro Arg Leu
465 470 475 480

Gly Ser Glu Pro Lys Ser Ser Pro Ala Gly Leu Ile Ala Ala Ala Asp
485 490 495

Gly Ser Cys Ala Gly Gly Glu Pro Ser Pro Trp Gln Asp Ser Lys Pro
500 505 510

Arg Glu His Pro Gly Leu Gly Gln Leu Glu Pro Pro His Cys His Tyr
515 520 525

Val Ala Pro Leu Gln Gly Ser Ser Asp Met Asn Gln Ser Trp Val Phe
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Thr Arg Val Ile Gly Val Ser Arg Glu Glu Ala Gly Ala Leu Glu Ala
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565 570 575

Ser Ser Tyr Thr Phe Ser Ser Ile Ala Arg Val Arg Met Glu Glu His
580 585 590

Phe Ile Gln Lys Ala Glu Gly Val Glu Pro Arg Leu Lys Gly Lys Val
595 600 605

Tyr Asp Tyr Tyr Val Glu Ser Thr Ser Gln Ala Ile Phe Gln Gly Arg
610 615 620

Leu Ala Pro Arg Thr Ala Ala Leu Thr Glu Val Pro Ser Pro Arg Pro
625 630 635 640

Pro Pro Gly Ser Leu Gly Thr Gly Ala Ala Ser Gly Gly Gln Ala Gly
645 650 655

Asp Thr Lys Gly Ala Ala Glu Arg Ala Ala Ser Pro Gln Thr Gly Pro
660 665 670

Trp Pro Ser Thr Arg Gly Phe Ser Arg Lys Glu Ser Leu Leu Gln Ile
675 680 685

Ala Glu Asn Pro Glu Leu Gln Leu Gln Pro Asp Gly Phe Arg Leu Pro
690 695 700

Ala Pro Pro Cys Pro Asp Pro Gly Ala Leu Pro Gly Leu Gly Arg Ser
705 710 715 720

Ser Arg Glu Pro His Val Gln Pro Val Ala Gly Thr Asn Phe Phe His
725 730 735

Ile Pro Leu Thr Pro Ala Ser Ala Pro Gln Val Arg Leu Asp Leu Gly
740 745 750

Asn Cys Tyr Glu Val Leu Thr Leu Ala Lys Arg Gln Asn Leu Glu Ala
755 760 765

Leu Lys Glu Ala Ala Tyr Lys Val Met Ser Glu Asn Tyr Leu Gln Val
770 775 780

Leu Arg Ser Pro Asp Ile Tyr Gly Cys Leu Ser Gly Ala Glu Arg Glu
785 790 795 800

Leu Ile Leu Gln Arg Arg Leu Arg Gly Arg Gln Tyr Leu Val Val Ala
805 810 815

Asp Val Cys Pro Lys Glu Asp Ser Gly Gly Leu Cys Cys Tyr Asp Asp
820 825 830

Glu Gln Asp Val Trp Arg Pro Leu Ala Arg Met Pro Pro Glu Ala Val
835 840 845

Ser Arg Gly Cys Ala Ile Cys Ser Leu Phe Asn Tyr Leu Phe Val Val
850 855 860

Ser Gly Cys Gln Gly Pro Gly His Gln Pro Ser Ser Arg Val Phe Cys
865 870 875 880

Tyr Asn Pro Leu Thr Gly Ile Trp Ser Glu Val Cys Pro Leu Asn Gln
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Ala Arg Pro His Cys Arg Leu Val Ala Leu Asp Gly His Leu Tyr Ala
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Ala His Thr Ala Thr Val Arg Ala Lys Glu Ile Phe Val Thr Gly Gly
945 950 955 960

Ser Leu Arg Phe Leu Leu Phe Arg Phe Ser Ala Gln Glu Gln Arg Trp
965 970 975

Trp Ala Gly Pro Thr Gly Gly Ser Lys Asp Arg Thr Ala Glu Met Val
980 985 990

Ala Val Asn Gly Phe Leu Tyr Arg Phe Asp Leu Asn Arg Ser Leu Gly
995 1000 1005

Ile Ala Val Tyr Arg Cys Ser Ala Ser Thr Arg Leu Trp Tyr Glu
1010 1015 1020

Cys Ala Thr Tyr Arg Thr Pro Tyr Pro Asp Ala Phe Gln Cys Ala
1025 1030 1035

Val Val Asp Asn Leu Ile Tyr Cys Val Gly Arg Arg Ser Thr Leu
1040 1045 1050

Cys Phe Leu Ala Asp Ser Val Ser Pro Arg Ser Val Ala Val Phe
1055 1060 1065

Leu Ser Gly Ser Trp Gly Asn His His Gln Ser Ala Leu Gln Gly
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Asp Ser Ile Ile Cys Pro Pro Cys Ala Arg Trp Ser Gln Leu Asp
1085 1090 1095

Pro Val Ser Thr Glu Ala Ala Gly Ala Gln Ala Val Gly Leu Val
1100 1105 1110

Gly Arg Ser Arg Thr Gly Thr Lys Asp Glu Lys Glu Val Gly Met
1115 1120 1125

Asp Ile Arg Gly Glu Leu Ala Leu Asp His Arg Arg Pro Pro Ser
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Ala Thr Gly
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cacacataca ccacagccac acactgtgca tacacgcaca ccccacaacc cacatactgc 180

atgcacacac acacacctac aagctgcatg ctgcatacac aagtcataca ggagataaac 240

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Met Gly Gly
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ttt cta cct aag gca gaa ggg ccc ggg agc caa ctc cag aaa ctt ctg 406
Phe Leu Pro Lys Ala Glu Gly Pro Gly Ser Gln Leu Gln Lys Leu Leu
5 10 15

ccc tcc ttt ctg gtc aga gaa caa gac tgg gac cag cac ctg gac aag 454
Pro Ser Phe Leu Val Arg Glu Gln Asp Trp Asp Gln His Leu Asp Lys
20 25 30 35

ctt cat atg ctg cag cag aag agg att cta gag tct cca ctg ctt cga 502
Leu His Met Leu Gln Gln Lys Arg Ile Leu Glu Ser Pro Leu Leu Arg
40 45 50

gca tcc aag gaa aat gac ctg tct gtt ctt agg caa ctt cta ctg gac 550
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55 60 65

tgc acc tgt gac gtt cga caa aga gga gcc ctg ggg gag acg gcg ctg 598
Cys Thr Cys Asp Val Arg Gln Arg Gly Ala Leu Gly Glu Thr Ala Leu
70 75 80

cac ata gca gcc ctc tat gac aac ttg gag gcg gcc ttg gtg ctg atg 646
His Ile Ala Ala Leu Tyr Asp Asn Leu Glu Ala Ala Leu Val Leu Met
85 90 95

gag gct gcc cca gag ctg gtc ttt gag ccc acc aca tgt gag gct ttt 694
Glu Ala Ala Pro Glu Leu Val Phe Glu Pro Thr Thr Cys Glu Ala Phe
100 105 110 115

gca ggt cag act gca ctg cac atc gct gtt gtg aac cag aat gtg aac 742
Ala Gly Gln Thr Ala Leu His Ile Ala Val Val Asn Gln Asn Val Asn
120 125 130

ctg gtg cgt gcc ctg ctc acc cgc agg gcc agt gtc tct gcc aga gcc 790
Leu Val Arg Ala Leu Leu Thr Arg Arg Ala Ser Val Ser Ala Arg Ala
135 140 145

aca ggc act gcc ttc cgc cgt agt ccc cgc aac ctc atc tac ttt ggg 838
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cgg ctg ctc att gag cat gga gct gac atc agg gcc cag gac tcc ctg 934
Arg Leu Leu Ile Glu His Gly Ala Asp Ile Arg Ala Gln Asp Ser Leu
180 185 190 195

gga aac aca gta tta cac atc ctc atc ctc cag ccc aac aaa acc ttt 982
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200 205 210

gcc tgc cag atg tac aac ctg ctg ctg tcc tac gat gga cat ggg gac 1030
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215 220 225

cac ctg cag ccc ctg gac ctt gtg ccc aat cac cag ggt ctc acc ccc 1078
His Leu Gln Pro Leu Asp Leu Val Pro Asn His Gln Gly Leu Thr Pro
230 235 240

ttc aag ctg gct gga gtg gag ggt aac act gtg atg ttc cag cac ctg 1126
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260                 265                 270                 275

att ctc tac gac ctc aca gag atc gac tcc tgg gga gag gag ctg tcc     1222
Ile Leu Tyr Asp Leu Thr Glu Ile Asp Ser Trp Gly Glu Glu Leu Ser
                280                 285                 290

ttc ctg gag ctt gtg gtc tcc tct gat aaa cga gag gct cgc caa att     1270
Phe Leu Glu Leu Val Val Ser Ser Asp Lys Arg Glu Ala Arg Gln Ile
            295                 300                 305

ctg gaa cag acc cca gtg aag gag ctg gtg agc ttc aag tgg aac aag     1318
Leu Glu Gln Thr Pro Val Lys Glu Leu Val Ser Phe Lys Trp Asn Lys
        310                 315                 320

tat ggc cgg ccg tac ttc tgc atc ctg gct gcc ttg tac ctg ctc tac     1366
Tyr Gly Arg Pro Tyr Phe Cys Ile Leu Ala Ala Leu Tyr Leu Leu Tyr
    325                 330                 335

atg atc tgc ttt acc acg tgc tgc gtc tac cgc ccc ctt aag ttt cgt     1414
Met Ile Cys Phe Thr Thr Cys Cys Val Tyr Arg Pro Leu Lys Phe Arg
340                 345                 350                 355

ggt ggc aac cgc act cat tct cga gac atc acc atc ctc cag caa aaa     1462
Gly Gly Asn Arg Thr His Ser Arg Asp Ile Thr Ile Leu Gln Gln Lys
                360                 365                 370

cta cta cag gag gcc tat gag aca cgt gaa gat atc atc agg ctg gtg     1510
Leu Leu Gln Glu Ala Tyr Glu Thr Arg Glu Asp Ile Ile Arg Leu Val
            375                 380                 385

ggg gag ctg gtg agc atc gtt ggg gct gtg atc atc ctg ctc cta gag     1558
Gly Glu Leu Val Ser Ile Val Gly Ala Val Ile Ile Leu Leu Leu Glu
        390                 395                 400

att cca gac atc ttc agg gtt ggt gcc tct cgc tat ttt gga aag acg     1606
Ile Pro Asp Ile Phe Arg Val Gly Ala Ser Arg Tyr Phe Gly Lys Thr
    405                 410                 415

att ctt ggg ggg cca ttc cat gtc atc atc atc acc tat gcc tcc ctg     1654
Ile Leu Gly Gly Pro Phe His Val Ile Ile Ile Thr Tyr Ala Ser Leu
420                 425                 430                 435

gtg ctg gtg acc atg gtg atg cgg ctc acc aac acc aat ggg gag gtg     1702
Val Leu Val Thr Met Val Met Arg Leu Thr Asn Thr Asn Gly Glu Val
                440                 445                 450

gtg ccc atg tcc ttt gcc ctg gtg ctg ggc tgg tgc agt gtc atg tat     1750
Val Pro Met Ser Phe Ala Leu Val Leu Gly Trp Cys Ser Val Met Tyr
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ttc act cga gga ttc cag atg ctg ggt ccc ttc acc atc atg atc cag     1798
Phe Thr Arg Gly Phe Gln Met Leu Gly Pro Phe Thr Ile Met Ile Gln
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aag atg att ttt gga gac cta atg cgt ttc tgc tgg ctg atg gct gtg     1846
Lys Met Ile Phe Gly Asp Leu Met Arg Phe Cys Trp Leu Met Ala Val
    485                 490                 495

gtc atc ttg gga ttt gcc tcc gcg ttc tat atc att ttc cag aca gag     1894
Val Ile Leu Gly Phe Ala Ser Ala Phe Tyr Ile Ile Phe Gln Thr Glu
500                 505                 510                 515

gac cca acc agt ctg ggg caa ttc tat gac tac ccc atg gca ctg ttc     1942
Asp Pro Thr Ser Leu Gly Gln Phe Tyr Asp Tyr Pro Met Ala Leu Phe
                520                 525                 530

acc acc ttt gag ctt ttt ctc act gtt att gat gca cct gcc aac tac     1990
Thr Thr Phe Glu Leu Phe Leu Thr Val Ile Asp Ala Pro Ala Asn Tyr
            535                 540                 545

gac gtg gac ttg ccc ttc atg ttc agc att gtc aac ttc gcc ttc gcc     2038
Asp Val Asp Leu Pro Phe Met Phe Ser Ile Val Asn Phe Ala Phe Ala
        550                 555                 560

atc att gcc aca ctg ctc atg ctc aac ttg ttc atc gcc atg atg ggc     2086
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cag gtc gtg gcc acc aca gtg atg ctg gag cgg aag ctg cct cgc tgc     2182
Gln Val Val Ala Thr Thr Val Met Leu Glu Arg Lys Leu Pro Arg Cys
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ctg tgg cct cgc tcc ggg atc tgt ggg tgc gaa ttc ggg ctg ggg gac     2230
Leu Trp Pro Arg Ser Gly Ile Cys Gly Cys Glu Phe Gly Leu Gly Asp
            615                 620                 625

cgc tgg ttc ctg cgg gtt gag aac cac aat gat cag aat cct ctg cga     2278
Arg Trp Phe Leu Arg Val Glu Asn His Asn Asp Gln Asn Pro Leu Arg
        630                 635                 640

gtg ctt cgc tat gtg gaa gtg ttc aag aac tca gac aag gag gat gac     2326
Val Leu Arg Tyr Val Glu Val Phe Lys Asn Ser Asp Lys Glu Asp Asp
    645                 650                 655

cag gag cat cca tct gag aaa cag ccc tct ggg gct gag agt ggg act     2374
Gln Glu His Pro Ser Glu Lys Gln Pro Ser Gly Ala Glu Ser Gly Thr
660                 665                 670                 675

cta gcc aga gcc tct ttg gct ctt cca act tcc tcc ctg tcc cgg acc     2422
Leu Ala Arg Ala Ser Leu Ala Leu Pro Thr Ser Ser Leu Ser Arg Thr
                680                 685                 690

gcg tcc cag agc agc agt cac cga ggc tgg gag atc ctt cgt caa aac     2470
Ala Ser Gln Ser Ser Ser His Arg Gly Trp Glu Ile Leu Arg Gln Asn
            695                 700                 705

acc ctg ggg cac ttg aat ctt gga ctg aac ctt agt gag ggg gat gga     2518
Thr Leu Gly His Leu Asn Leu Gly Leu Asn Leu Ser Glu Gly Asp Gly
        710                 715                 720

gag gag gtc tac cat ttt tgattaacat cgctatcact cttgaccttа            2566
Glu Glu Val Tyr His Phe
    725

ctcccggttg gcctgggggc ggggacagag acggagacct ctgcctatgc aagtgtctaa   2626

cttctgtgcc tgttaatcat gggagggtga gacagaacaa tccctaaagg gtcatgcctc   2686

acacttcaca tcagaatttc tggcaatggg caatggtcat cgattgtctc acgtattttc   2746

tgggctcttg caagtcaccc atctcaggaa aaaggaggtt ggcaactaaa gacatgaggc   2806

agggatgcta gattaatgtc aggacccatt tctcttctgc cccacgcagc ccctagaaag   2866

tagtaagctg tgaggctatt ctggctcccc agggcttacg tgggaagagc caggcatggc   2926

atagaggttg tggcccttct ttttttc                                       2953


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<213>  Homo sapiens

<400>  101

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1               5                   10                  15

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            20                  25                  30

Leu Asp Lys Leu His Met Leu Gln Gln Lys Arg Ile Leu Glu Ser Pro
        35                  40                  45

Leu Leu Arg Ala Ser Lys Glu Asn Asp Leu Ser Val Leu Arg Gln Leu
    50                  55                  60
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Leu Leu Asp Cys Thr Cys Asp Val Arg Gln Arg Gly Ala Leu Gly Glu
65 70 75 80

Thr Ala Leu His Ile Ala Ala Leu Tyr Asp Asn Leu Glu Ala Ala Leu
85 90 95

Val Leu Met Glu Ala Ala Pro Glu Leu Val Phe Glu Pro Thr Thr Cys
100 105 110

Glu Ala Phe Ala Gly Gln Thr Ala Leu His Ile Ala Val Val Asn Gln
115 120 125

Asn Val Asn Leu Val Arg Ala Leu Leu Thr Arg Arg Ala Ser Val Ser
130 135 140

Ala Arg Ala Thr Gly Thr Ala Phe Arg Arg Ser Pro Arg Asn Leu Ile
145 150 155 160

Tyr Phe Gly Glu His Pro Leu Ser Phe Ala Ala Cys Val Asn Ser Glu
165 170 175

Glu Ile Val Arg Leu Leu Ile Glu His Gly Ala Asp Ile Arg Ala Gln
180 185 190

Asp Ser Leu Gly Asn Thr Val Leu His Ile Leu Ile Leu Gln Pro Asn
195 200 205

Lys Thr Phe Ala Cys Gln Met Tyr Asn Leu Leu Leu Ser Tyr Asp Gly
210 215 220

His Gly Asp His Leu Gln Pro Leu Asp Leu Val Pro Asn His Gln Gly
225 230 235 240

Leu Thr Pro Phe Lys Leu Ala Gly Val Glu Gly Asn Thr Val Met Phe
245 250 255

Gln His Leu Met Gln Lys Arg Arg His Ile Gln Trp Thr Tyr Gly Pro
260 265 270

Leu Thr Ser Ile Leu Tyr Asp Leu Thr Glu Ile Asp Ser Trp Gly Glu
275 280 285

Glu Leu Ser Phe Leu Glu Leu Val Val Ser Ser Asp Lys Arg Glu Ala
290 295 300

Arg Gln Ile Leu Glu Gln Thr Pro Val Lys Glu Leu Val Ser Phe Lys
305 310 315 320

Trp Asn Lys Tyr Gly Arg Pro Tyr Phe Cys Ile Leu Ala Ala Leu Tyr
325 330 335

Leu Leu Tyr Met Ile Cys Phe Thr Thr Cys Cys Val Tyr Arg Pro Leu
340 345 350

Lys Phe Arg Gly Gly Asn Arg Thr His Ser Arg Asp Ile Thr Ile Leu
355 360 365

Gln Gln Lys Leu Leu Gln Glu Ala Tyr Glu Thr Arg Glu Asp Ile Ile
370 375 380

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Arg Leu Val Gly Glu Leu Val Ser Ile Val Gly Ala Val Ile Ile Leu
385 390 395 400

Leu Leu Glu Ile Pro Asp Ile Phe Arg Val Gly Ala Ser Arg Tyr Phe
405 410 415

Gly Lys Thr Ile Leu Gly Gly Pro Phe His Val Ile Ile Ile Thr Tyr
420 425 430

Ala Ser Leu Val Leu Val Thr Met Val Met Arg Leu Thr Asn Thr Asn
435 440 445

Gly Glu Val Val Pro Met Ser Phe Ala Leu Val Leu Gly Trp Cys Ser
450 455 460

Val Met Tyr Phe Thr Arg Gly Phe Gln Met Leu Gly Pro Phe Thr Ile
465 470 475 480

Met Ile Gln Lys Met Ile Phe Gly Asp Leu Met Arg Phe Cys Trp Leu
485 490 495

Met Ala Val Val Ile Leu Gly Phe Ala Ser Ala Phe Tyr Ile Ile Phe
500 505 510

Gln Thr Glu Asp Pro Thr Ser Leu Gly Gln Phe Tyr Asp Tyr Pro Met
515 520 525

Ala Leu Phe Thr Thr Phe Glu Leu Phe Leu Thr Val Ile Asp Ala Pro
530 535 540

Ala Asn Tyr Asp Val Asp Leu Pro Phe Met Phe Ser Ile Val Asn Phe
545 550 555 560

Ala Phe Ala Ile Ile Ala Thr Leu Leu Met Leu Asn Leu Phe Ile Ala
565 570 575

Met Met Gly Asp Thr His Trp Arg Val Ala Gln Glu Arg Asp Glu Leu
580 585 590

Trp Arg Ala Gln Val Val Ala Thr Thr Val Met Leu Glu Arg Lys Leu
595 600 605

Pro Arg Cys Leu Trp Pro Arg Ser Gly Ile Cys Gly Cys Glu Phe Gly
610 615 620

Leu Gly Asp Arg Trp Phe Leu Arg Val Glu Asn His Asn Asp Gln Asn
625 630 635 640

Pro Leu Arg Val Leu Arg Tyr Val Glu Val Phe Lys Asn Ser Asp Lys
645 650 655

Glu Asp Asp Gln Glu His Pro Ser Glu Lys Gln Pro Ser Gly Ala Glu
660 665 670

Ser Gly Thr Leu Ala Arg Ala Ser Leu Ala Leu Pro Thr Ser Ser Leu
675 680 685

Ser Arg Thr Ala Ser Gln Ser Ser Ser His Arg Gly Trp Glu Ile Leu

DCID: <WO___ ___03089583A2 I_>

690 695 700

Arg Gln Asn Thr Leu Gly His Leu Asn Leu Gly Leu Asn Leu Ser Glu
705 710 715 720

Gly Asp Gly Glu Glu Val Tyr His Phe
725

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<211> 1545
<212> DNA
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<222> (130)..(438)
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<400> 102
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accaccacca accagacgat ctgcttcaga gacctgggcc aggcccatgt gcccgggctg 120

gccgtgggc atg ggc ctg gta cgc agc gtg ggc gcc ttg gcc gtg gtg gcc 171
Met Gly Leu Val Arg Ser Val Gly Ala Leu Ala Val Val Ala
1 5 10

gcc att ttt ggc ctg gag ttc ctc atg gtg tcc cag ttg tgc gag gac 219
Ala Ile Phe Gly Leu Glu Phe Leu Met Val Ser Gln Leu Cys Glu Asp
15 20 25 30

aaa cac tca cag tgc aag tgg gtc atg ggt tcc atc ctc ctc ctg gtg 267
Lys His Ser Gln Cys Lys Trp Val Met Gly Ser Ile Leu Leu Leu Val
35 40 45

tct ttc gtc ctc tcc tcc ggc ggg ctc ctg ggt ttt gtg atc ctc ctc 315
Ser Phe Val Leu Ser Ser Gly Gly Leu Leu Gly Phe Val Ile Leu Leu
50 55 60

agg aac caa gtc aca ctc atc ggc ttc acc cta atg ttt tgg tgc gaa 363
Arg Asn Gln Val Thr Leu Ile Gly Phe Thr Leu Met Phe Trp Cys Glu
65 70 75

ttc act gcc tcc ttc ctc ctc ttc ctg aac gcc atc agc ggc ctt cac 411
Phe Thr Ala Ser Phe Leu Leu Phe Leu Asn Ala Ile Ser Gly Leu His
80 85 90

atc aac agc atc acc cat ccc tgg gaa tgaccgtgga aattttaggc 458
Ile Asn Ser Ile Thr His Pro Trp Glu
95 100

cccctccagg gacatcagat tccacaagaa aatatggtca aaatgggact tttccagcat 518

gtggcctctg gtggggctgg gttggacaag ggccttgaaa cggctgcctg tttgccgata 578

acttgtgggt ggtcagccag aaatggcccg ggggcctctg cacctggtct gcagggccag 638

aggccaggag ggtgcctcag tgccaccaac tgcacaggct tagccagatg ttgattttag 698

aggaagaaaa aaacatttta aaactccttc ttgaattttc ttccctggac tggaatacag 758

ttggaagcac aggggtaact ggtacctgag ctagctgcac agccaaggat agttcatgcc 818

tgtttcattg acacgtgctg ggataggggc tgcagaatcc ctggggctcc cagggttgtt 878

aagaatggat cattcttcca gctaagggtc caatcagtgc ctaggacttt cttccaccag 938

ctcaaagggc cttcgtatgt atgtccctgg cttcagcttt ggtcatgcca aagaggcaga 998

gttcaggatt ccctcagaat gccctgcaca cagtaggttt ccaaaccatt tgactcggtt 1058

tgcctccctg cccgttgttt aaaccttaca aaccctggat aaccccatct tctagcagct 1118

ggctgtgcct ctgggagctc tgcctatcag aaccctacct taaggtgggt ttccttccga 1178

gaagagttct tgagcaagct ctcccaggag ggcccacctg actgctaata cacagccctc 1238

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atttttaatc ccagaacaca tttcaaagag cacgtatcta gacctgctgg actctgcagg 1358

gggtgagggg gaacagcgag agcttgggta atgattaaca cccatgctgg ggatgcatgg 1418

aggtgaaggg ggccaggaac cagtggagat ttccatcctt gccagcacgt ctgtacttct 1478

gttcattaaa gtgctccctt tctagtcgat gtgtcactgc tgtatcatac ttttatgcta 1538

cacaacc 1545

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<212> PRT
<213> Homo sapiens

<400> 103

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Phe Gly Leu Glu Phe Leu Met Val Ser Gln Leu Cys Glu Asp Lys His
20 25 30

Ser Gln Cys Lys Trp Val Met Gly Ser Ile Leu Leu Leu Val Ser Phe
35 40 45

Val Leu Ser Ser Gly Gly Leu Leu Gly Phe Val Ile Leu Leu Arg Asn
50 55 60

Gln Val Thr Leu Ile Gly Phe Thr Leu Met Phe Trp Cys Glu Phe Thr
65 70 75 80

Ala Ser Phe Leu Leu Phe Leu Asn Ala Ile Ser Gly Leu His Ile Asn
85 90 95

Ser Ile Thr His Pro Trp Glu
100

<210> 104
<211> 24
<212> DNA
<213> Homo sapiens

<400> 104
gcgcttccgg acctgtatct ccac 24

<210> 105
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<212> DNA
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<400> 105
caagctctgg gtctcgggca gaag 24

<210> 106
<211> 50
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aaagagcctc taaagaaggg ttccagacta ccaggagctc actggaaata 50

<210> 107
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<213> Homo sapiens

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<210> 108
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<400> 108
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<210> 109
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<210> 110
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<210> 112
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<400> 112
aagtgtaaag catgccccgc ctga 24

<210> 113
<211> 50
<212> DNA
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<400> 113
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<210> 114
<211> 50
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<400> 114
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<210> 115
<211> 24
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gttcgctatg ctgccacggt catc 24

<210> 116

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<400> 116
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<210> 117
<211> 50
<212> DNA
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<400> 117
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<210> 118
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<212> DNA
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<400> 118
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<210> 119
<211> 24
<212> DNA
<213> Homo sapiens

<400> 119
caggattacg cacaaacggc atgg 24

<210> 120
<211> 24
<212> DNA
<213> Homo sapiens

<400> 120
tgggaggcag agatagcaga gccc 24

<210> 121
<211> 50
<212> DNA
<213> Homo sapiens

<400> 121
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<210> 122
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<212> DNA
<213> Homo sapiens

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ctggtcctgg gcaccctgat aagc 24

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<400> 123
cccaggtctg gttgcagtgc tctc 24

<210> 124
<211> 50
<212> DNA
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<400> 124
agctgtcctc attaaaagtg acctggagtg agatggattc ttctgcctat 50

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<211> 50
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<210> 126
<211> 24
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<400> 126
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<210> 127
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<400> 127
tacggccgag aagcactgga gatg 24

<210> 128
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<210> 131
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<400> 131
gtcacctcag cgatctcaac gataggg 27

<210> 132
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<400> 132
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<210> 133
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<212> DNA
<213> Homo sapiens

<400> 133

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<212> DNA
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<400> 134
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<210> 135
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<212> DNA
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<400> 135
gggtgggaag gaagcaggga agag 24

<210> 136
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<212> DNA
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<400> 136
ccagctagtt catgcttggc gcag 24

<210> 137
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<400> 137
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<210> 138
<211> 30
<212> DNA
<213> Homo sapiens

<400> 138
ctgttgggaa tcttcagcca gatctcacac 30

<210> 139
<211> 24
<212> DNA
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<400> 139
atggaggttt ctgcacgctc agca 24

<210> 140
<211> 50
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aagcaatttg ttaaaaactg gcattacttt actcttatgc tttctgtgtc 50

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<210> 142
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<400> 143
tggcctgaga ggtagattcc acatagtagt cgt 33

<210> 144
<211> 50
<212> DNA
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<400> 144
aaggcttctt caaaaaaagc gggcttgttc tgggccagaa aatcagagtg 50

<210> 145
<211> 31
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<213> Homo sapiens

<400> 145
ctcctttctg gtcagagaac aagactggga c 31

<210> 146
<211> 27
<212> DNA
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<400> 146
gtgatgtctc gagaatgagt gcggttg 27

<210> 147
<211> 50
<212> DNA
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<400> 147
cagcgaggca gaaaaatgtc ccacaagttg agccctcccc actcccagtg 50

<210> 148
<211> 50
<212> DNA
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<400> 148
taatataaaa tatataaaat agtgcaacat tacttattcc tcctggtgtt 50

<210> 149
<211> 27
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<400> 149
gcagatgacc cgacctgact gttcttc 27

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<210> 151
<211> 50

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<212> DNA
<213> Homo sapiens

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<210> 152
<211> 945
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(945)
<223>

<400> 152
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1 5 10 15

tta act gaa caa gca gag ctt cag ctg ccc ctc ttc tgc ctc ttc tta 96
Leu Thr Glu Gln Ala Glu Leu Gln Leu Pro Leu Phe Cys Leu Phe Leu
20 25 30

gga att tac aca gtt act gtg gtg gga aac ctc agc atg atc tca att 144
Gly Ile Tyr Thr Val Thr Val Val Gly Asn Leu Ser Met Ile Ser Ile
35 40 45

att agg ctg aat cgt caa ctt cat acc ccc atg tac tat ttc ctg agt 192
Ile Arg Leu Asn Arg Gln Leu His Thr Pro Met Tyr Tyr Phe Leu Ser
50 55 60

agt ttg tct ttt tta gat ttc tgc tat tct tct gtc att acc cct aaa 240
Ser Leu Ser Phe Leu Asp Phe Cys Tyr Ser Ser Val Ile Thr Pro Lys
65 70 75 80

atg cta tca ggg ttt tta tgc aga gat aga tcc atc tcc tat tct gga 288
Met Leu Ser Gly Phe Leu Cys Arg Asp Arg Ser Ile Ser Tyr Ser Gly
85 90 95

tgc atg att cag ctg ttt ttt ttc tgt gtt tgt gtt att tct gaa tgc 336
Cys Met Ile Gln Leu Phe Phe Phe Cys Val Cys Val Ile Ser Glu Cys
100 105 110

tac atg ctg gca gcc atg gcc tgc gat cgc tac gtg gcc atc tgc agc 384
Tyr Met Leu Ala Ala Met Ala Cys Asp Arg Tyr Val Ala Ile Cys Ser
115 120 125

cca ctg ctc tac agg gtc atc atg tcc cct agg gtc tgt tct ctg ctg 432
Pro Leu Leu Tyr Arg Val Ile Met Ser Pro Arg Val Cys Ser Leu Leu
130 135 140

gtg gct gct gtc ttc tca gta ggt ttc act gat gct gtg atc cat gga 480
Val Ala Ala Val Phe Ser Val Gly Phe Thr Asp Ala Val Ile His Gly
145 150 155 160

ggt tgt ata ctc agg ttg tct ttc tgt gga tca aac atc att aaa cat 528
Gly Cys Ile Leu Arg Leu Ser Phe Cys Gly Ser Asn Ile Ile Lys His
165 170 175

tat ttc tgt gac att gtc cct ctt att aaa ctc tcc tgc tcc agc act 576
Tyr Phe Cys Asp Ile Val Pro Leu Ile Lys Leu Ser Cys Ser Ser Thr
180 185 190

tat att gat gag ctt ttg att ttt gtc att ggt gga ttt aac atg gtg 624
Tyr Ile Asp Glu Leu Leu Ile Phe Val Ile Gly Gly Phe Asn Met Val
195 200 205

gcc aca agc cta aca atc att att tca tat gct ttt atc ctc acc agc 672
Ala Thr Ser Leu Thr Ile Ile Ile Ser Tyr Ala Phe Ile Leu Thr Ser
210 215 220

atc ctg cgc atc cac tct aaa aag ggc agg tgc aaa gcg ttt agc acc 720
Ile Leu Arg Ile His Ser Lys Lys Gly Arg Cys Lys Ala Phe Ser Thr
225 230 235 240

tgt agc tcc cac ctg aca gct gtt ctt atg ttt tat ggg tct ctg atg 768

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Cys Ser Ser His Leu Thr Ala Val Leu Met Phe Tyr Gly Ser Leu Met
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tcc atg tat ctc aaa cct gct tct agc agt tca ctc acc cag gag aaa      816
Ser Met Tyr Leu Lys Pro Ala Ser Ser Ser Ser Leu Thr Gln Glu Lys
            260                 265                 270

gta tcc tca gta ttt tat acc act gtg att ctc atg ttg aat ccc ttg      864
Val Ser Ser Val Phe Tyr Thr Thr Val Ile Leu Met Leu Asn Pro Leu
        275                 280                 285

ata tat agt ctg agg aac aat gaa gta aga aat gct ctg atg aaa ctt      912
Ile Tyr Ser Leu Arg Asn Asn Glu Val Arg Asn Ala Leu Met Lys Leu
    290                 295                 300

tta aga aga aaa ata tct tta tct cca gga taa                         945
Leu Arg Arg Lys Ile Ser Leu Ser Pro Gly
305                 310


<210>  153
<211>  314
<212>  PRT
<213>  Homo sapiens

<400>  153

Met Gly Val Lys Asn His Ser Thr Val Thr Glu Phe Leu Leu Ser Gly
1               5                   10                  15

Leu Thr Glu Gln Ala Glu Leu Gln Leu Pro Leu Phe Cys Leu Phe Leu
            20                  25                  30

Gly Ile Tyr Thr Val Thr Val Val Gly Asn Leu Ser Met Ile Ser Ile
        35                  40                  45

Ile Arg Leu Asn Arg Gln Leu His Thr Pro Met Tyr Tyr Phe Leu Ser
    50                  55                  60

Ser Leu Ser Phe Leu Asp Phe Cys Tyr Ser Ser Val Ile Thr Pro Lys
65                  70                  75                  80

Met Leu Ser Gly Phe Leu Cys Arg Asp Arg Ser Ile Ser Tyr Ser Gly
                85                  90                  95

Cys Met Ile Gln Leu Phe Phe Phe Cys Val Cys Val Ile Ser Glu Cys
            100                 105                 110

Tyr Met Leu Ala Ala Met Ala Cys Asp Arg Tyr Val Ala Ile Cys Ser
        115                 120                 125

Pro Leu Leu Tyr Arg Val Ile Met Ser Pro Arg Val Cys Ser Leu Leu
    130                 135                 140

Val Ala Ala Val Phe Ser Val Gly Phe Thr Asp Ala Val Ile His Gly
145                 150                 155                 160

Gly Cys Ile Leu Arg Leu Ser Phe Cys Gly Ser Asn Ile Ile Lys His
                165                 170                 175

Tyr Phe Cys Asp Ile Val Pro Leu Ile Lys Leu Ser Cys Ser Ser Thr
            180                 185                 190

Tyr Ile Asp Glu Leu Leu Ile Phe Val Ile Gly Gly Phe Asn Met Val
        195                 200                 205
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Ala Thr Ser Leu Thr Ile Ile Ile Ser Tyr Ala Phe Ile Leu Thr Ser
210 215 220

Ile Leu Arg Ile His Ser Lys Lys Gly Arg Cys Lys Ala Phe Ser Thr
225 230 235 240

Cys Ser Ser His Leu Thr Ala Val Leu Met Phe Tyr Gly Ser Leu Met
245 250 255

Ser Met Tyr Leu Lys Pro Ala Ser Ser Ser Ser Leu Thr Gln Glu Lys
260 265 270

Val Ser Ser Val Phe Tyr Thr Thr Val Ile Leu Met Leu Asn Pro Leu
275 280 285

Ile Tyr Ser Leu Arg Asn Asn Glu Val Arg Asn Ala Leu Met Lys Leu
290 295 300

Leu Arg Arg Lys Ile Ser Leu Ser Pro Gly
305 310

<210> 154
<211> 34
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<213> Homo sapiens

<400> 154
ctgtgatcca tggaggttgt atactcaggt tgtc 34

<210> 155
<211> 36
<212> DNA
<213> Homo sapiens

<400> 155
tcatcagagc atttcttact tcattgttcc tcagac 36

<210> 156
<211> 50
<212> DNA
<213> Homo sapiens

<400> 156
caggagaatt aaatataaga gtggtcagtg tgtttgtaac actcaggaca 50

<210> 157
<211> 50
<212> DNA
<213> Homo sapiens

<400> 157
aaaacatgct ttaaaaaacc catgatatta aagacaaaaa actgagcata 50

<210> 158
<211> 50
<212> DNA
<213> Homo sapiens

<400> 158
atgaacagct tattaaatag ccaggtagct gggcagaatg agaaaatgca 50

<210> 159
<211> 50
<212> DNA
<213> Homo sapiens

<400> 159

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<211> 50
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<213> Homo sapiens

<400> 160
tgctataaaa tgtttttaaa aagtgtgaag ttggcctatc accaagtaag 50

<210> 161
<211> 50
<212> DNA
<213> Homo sapiens

<400> 161
taaatattgt atttatatag tccttcagga ggactgaggc atcctccagt 50

<210> 162
<211> 957
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(957)
<223>

<400> 162

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atg aat cca gca aat cat tcc cag gtg gca gga ttt gtt cta ctg ggg      48
Met Asn Pro Ala Asn His Ser Gln Val Ala Gly Phe Val Leu Leu Gly
1               5                  10                  15

ctc tct cag gtt tgg gag ctt cgg ttt gtt ttc ttc act gtt ttc tct      96
Leu Ser Gln Val Trp Glu Leu Arg Phe Val Phe Phe Thr Val Phe Ser
            20                  25                  30

gct gtg tat ttt atg act gta gtg gga aac ctt ctt att gtg gtc ata     144
Ala Val Tyr Phe Met Thr Val Val Gly Asn Leu Leu Ile Val Val Ile
        35                  40                  45

gtg acc tcc gac cca cac ctg cac aca acc atg tat ttt ctc ttg ggc     192
Val Thr Ser Asp Pro His Leu His Thr Thr Met Tyr Phe Leu Leu Gly
    50                  55                  60

aat ctt tct ttc ctg gac ttt tgc tac tct tcc atc aca gca cct agg     240
Asn Leu Ser Phe Leu Asp Phe Cys Tyr Ser Ser Ile Thr Ala Pro Arg
65                  70                  75                  80

atg ctg gtt gac ttg ctc tca ggc aac cct acc att tcc ttt ggt gga     288
Met Leu Val Asp Leu Leu Ser Gly Asn Pro Thr Ile Ser Phe Gly Gly
                85                  90                  95

tgc ctg act caa ctc ttc ttc ttc cac ttc att gga ggc atc aag atc     336
Cys Leu Thr Gln Leu Phe Phe Phe His Phe Ile Gly Gly Ile Lys Ile
            100                 105                 110

ttc ctg ctg act gtc atg gcg tat gac cgc tac att gcc att tcc cag     384
Phe Leu Leu Thr Val Met Ala Tyr Asp Arg Tyr Ile Ala Ile Ser Gln
        115                 120                 125

ccc ctg cac tac acg ctc att atg aat cag act gtc tgt gca ctc ctt     432
Pro Leu His Tyr Thr Leu Ile Met Asn Gln Thr Val Cys Ala Leu Leu
    130                 135                 140

atg gca gcc tcc tgg gtg ggg ggc ttc atc cac tcc ata gta cag att     480
Met Ala Ala Ser Trp Val Gly Gly Phe Ile His Ser Ile Val Gln Ile
145                 150                 155                 160

gca ttg act atc cag ctg cca ttc tgt ggg cct gac aag ctg gac aac     528
Ala Leu Thr Ile Gln Leu Pro Phe Cys Gly Pro Asp Lys Leu Asp Asn
                165                 170                 175

ttt tat tgt gat gtg cct cag ctg atc aaa ttg gcc tgc aca gat acc     576
Phe Tyr Cys Asp Val Pro Gln Leu Ile Lys Leu Ala Cys Thr Asp Thr
            180                 185                 190
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ttt gtc tta gag ctt tta atg gtg tct aac aat ggc ctg gtg acc ctg      624
Phe Val Leu Glu Leu Leu Met Val Ser Asn Asn Gly Leu Val Thr Leu
        195                 200                 205

atg tgt ttt ctg gtg ctt ctg gga tcg tac aca gca ctg cta gtc atg      672
Met Cys Phe Leu Val Leu Leu Gly Ser Tyr Thr Ala Leu Leu Val Met
    210                 215                 220

ctc cga agc cac tca cgg gag ggc cgc agc aag gcc ctg tct acc tgt      720
Leu Arg Ser His Ser Arg Glu Gly Arg Ser Lys Ala Leu Ser Thr Cys
225                 230                 235                 240

gcc tct cac att gct gtg gtg acc tta atc ttt gtg cct tgc atc tac      768
Ala Ser His Ile Ala Val Val Thr Leu Ile Phe Val Pro Cys Ile Tyr
                245                 250                 255

gtc tat aca agg cct ttt cgg aca ttc ccc atg gac aag gcc gtc tct      816
Val Tyr Thr Arg Pro Phe Arg Thr Phe Pro Met Asp Lys Ala Val Ser
            260                 265                 270

gtg cta tac aca att gtc acc ccc atg ctg aat cct gcc atc tat acc      864
Val Leu Tyr Thr Ile Val Thr Pro Met Leu Asn Pro Ala Ile Tyr Thr
        275                 280                 285

ctg aga aac aag gaa gtg atc atg gcc atg aag aag ctg tgg agg agg      912
Leu Arg Asn Lys Glu Val Ile Met Ala Met Lys Lys Leu Trp Arg Arg
    290                 295                 300

aaa aag gac cct att ggt ccc ctg gag cac aga ccc tta cat tag          957
Lys Lys Asp Pro Ile Gly Pro Leu Glu His Arg Pro Leu His
305                 310                 315
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<210> 163
<211> 318
<212> PRT
<213> Homo sapiens

<400> 163

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Met Asn Pro Ala Asn His Ser Gln Val Ala Gly Phe Val Leu Leu Gly
1               5                   10                  15

Leu Ser Gln Val Trp Glu Leu Arg Phe Val Phe Phe Thr Val Phe Ser
            20                  25                  30

Ala Val Tyr Phe Met Thr Val Val Gly Asn Leu Leu Ile Val Val Ile
        35                  40                  45

Val Thr Ser Asp Pro His Leu His Thr Thr Met Tyr Phe Leu Leu Gly
    50                  55                  60

Asn Leu Ser Phe Leu Asp Phe Cys Tyr Ser Ser Ile Thr Ala Pro Arg
65                  70                  75                  80

Met Leu Val Asp Leu Leu Ser Gly Asn Pro Thr Ile Ser Phe Gly Gly
                85                  90                  95

Cys Leu Thr Gln Leu Phe Phe Phe His Phe Ile Gly Gly Ile Lys Ile
            100                 105                 110

Phe Leu Leu Thr Val Met Ala Tyr Asp Arg Tyr Ile Ala Ile Ser Gln
        115                 120                 125

Pro Leu His Tyr Thr Leu Ile Met Asn Gln Thr Val Cys Ala Leu Leu
    130                 135                 140

Met Ala Ala Ser Trp Val Gly Gly Phe Ile His Ser Ile Val Gln Ile
145                 150                 155                 160
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Ala Leu Thr Ile Gln Leu Pro Phe Cys Gly Pro Asp Lys Leu Asp Asn
165 170 175

Phe Tyr Cys Asp Val Pro Gln Leu Ile Lys Leu Ala Cys Thr Asp Thr
180 185 190

Phe Val Leu Glu Leu Leu Met Val Ser Asn Asn Gly Leu Val Thr Leu
195 200 205

Met Cys Phe Leu Val Leu Leu Gly Ser Tyr Thr Ala Leu Leu Val Met
210 215 220

Leu Arg Ser His Ser Arg Glu Gly Arg Ser Lys Ala Leu Ser Thr Cys
225 230 235 240

Ala Ser His Ile Ala Val Val Thr Leu Ile Phe Val Pro Cys Ile Tyr
245 250 255

Val Tyr Thr Arg Pro Phe Arg Thr Phe Pro Met Asp Lys Ala Val Ser
260 265 270

Val Leu Tyr Thr Ile Val Thr Pro Met Leu Asn Pro Ala Ile Tyr Thr
275 280 285

Leu Arg Asn Lys Glu Val Ile Met Ala Met Lys Lys Leu Trp Arg Arg
290 295 300

Lys Lys Asp Pro Ile Gly Pro Leu Glu His Arg Pro Leu His
305 310 315

<210> 164
<211> 26
<212> DNA
<213> Homo sapiens

<400> 164
gaatccagca aatcattccc aggtgg 26

<210> 165
<211> 29
<212> DNA
<213> Homo sapiens

<400> 165
ctaatgtaag ggtctgtgct ccaggggac 29

<210> 166
<211> 50
<212> DNA
<213> Homo sapiens

<400> 166
cactaccctt ttaaagtgca gggggcagtg atttcttttc ttttcttttt 50

<210> 167
<211> 972
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(972)
<223>

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<400> 167

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atg aac cct gaa aac tgg act cag gta aca agc ttt gtc ctt ctg ggt       48
Met Asn Pro Glu Asn Trp Thr Gln Val Thr Ser Phe Val Leu Leu Gly
1               5                  10                  15

ttc ccc agt agc cac ctc ata cag ttc ctg gtg ttc ctg ggg tta atg       96
Phe Pro Ser Ser His Leu Ile Gln Phe Leu Val Phe Leu Gly Leu Met
            20                  25                  30

gtg acc tac att gta aca gcc aca ggc aag ctg cta att att gtg ctc      144
Val Thr Tyr Ile Val Thr Ala Thr Gly Lys Leu Leu Ile Ile Val Leu
        35                  40                  45

agc tgg ata gac caa cgc ctg cac ata cag atg tac ttc ttc ctg cgg      192
Ser Trp Ile Asp Gln Arg Leu His Ile Gln Met Tyr Phe Phe Leu Arg
    50                  55                  60

aat ttc tcc ttc ctg gag ctg ttg ctg gta act gtt gtg gtt ccc aag      240
Asn Phe Ser Phe Leu Glu Leu Leu Leu Val Thr Val Val Val Pro Lys
65                  70                  75                  80

atg ctt gtc gtc atc ctc acg ggg gat cac acc atc tca ttt gtc agc      288
Met Leu Val Val Ile Leu Thr Gly Asp His Thr Ile Ser Phe Val Ser
                85                  90                  95

tgc atc atc cag tcc tac ctc tac ttc ttt cta ggc acc act gac ttc      336
Cys Ile Ile Gln Ser Tyr Leu Tyr Phe Phe Leu Gly Thr Thr Asp Phe
            100                 105                 110

ttc ctc ttg gcc gtc atg tct ctg gat cgt tac ctg gca atc tgc cga      384
Phe Leu Leu Ala Val Met Ser Leu Asp Arg Tyr Leu Ala Ile Cys Arg
        115                 120                 125

cca ctc cgc tat gag acc ctg atg aat ggc cat gtc tgt tcc caa cta      432
Pro Leu Arg Tyr Glu Thr Leu Met Asn Gly His Val Cys Ser Gln Leu
    130                 135                 140

gtg ctg gcc tcc tgg cta gct gga ttc ctc tgg gtc ctt tgc ccc act      480
Val Leu Ala Ser Trp Leu Ala Gly Phe Leu Trp Val Leu Cys Pro Thr
145                 150                 155                 160

gtc ctc atg gcc agc ctg cct ttc tgt ggc ccc aat ggt att gac cac      528
Val Leu Met Ala Ser Leu Pro Phe Cys Gly Pro Asn Gly Ile Asp His
                165                 170                 175

ttc ttt cgt gac agt tgg ccc ttg ctc agg ctt tct tgt ggg gac acc      576
Phe Phe Arg Asp Ser Trp Pro Leu Leu Arg Leu Ser Cys Gly Asp Thr
            180                 185                 190

cac ctg ctg aaa ctg gtg gct ttc atg ctc tct acg ttg gtg tta ctg      624
His Leu Leu Lys Leu Val Ala Phe Met Leu Ser Thr Leu Val Leu Leu
        195                 200                 205

ggc tca ctg gct ctg acc tca gtt tcc tat gcc tgc att ctt gcc act      672
Gly Ser Leu Ala Leu Thr Ser Val Ser Tyr Ala Cys Ile Leu Ala Thr
    210                 215                 220

gtt ctc agg gcc cct aca gct gct gag cga agg aaa gcg ttt tcc act      720
Val Leu Arg Ala Pro Thr Ala Ala Glu Arg Arg Lys Ala Phe Ser Thr
225                 230                 235                 240

tgc gcc tcg cat ctt aca gtg gtg gtc atc atc tat ggc agt tcc atc      768
Cys Ala Ser His Leu Thr Val Val Val Ile Ile Tyr Gly Ser Ser Ile
                245                 250                 255

ttt ctc tac att cgt atg tca gag gct cag tcc aaa ctg ctc aac aaa      816
Phe Leu Tyr Ile Arg Met Ser Glu Ala Gln Ser Lys Leu Leu Asn Lys
            260                 265                 270

ggt gcc tcc gtc ctg agc tgc atc atc aca ccc ctc ttg aac cca ttc      864
Gly Ala Ser Val Leu Ser Cys Ile Ile Thr Pro Leu Leu Asn Pro Phe
        275                 280                 285

atc ttc act ctc cgc aat gac aag gtg cag caa gca ctg aga gaa gcc      912
Ile Phe Thr Leu Arg Asn Asp Lys Val Gln Gln Ala Leu Arg Glu Ala
    290                 295                 300

ttg ggg tgg ccc agg ctc act gct gtg atg aaa ctg agg gtc aca agt      960
Leu Gly Trp Pro Arg Leu Thr Ala Val Met Lys Leu Arg Val Thr Ser
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305 310 315 320

caa agg aaa tga 972
Gln Arg Lys

<210> 168
<211> 323
<212> PRT
<213> Homo sapiens

<400> 168

Met Asn Pro Glu Asn Trp Thr Gln Val Thr Ser Phe Val Leu Leu Gly
1 5 10 15

Phe Pro Ser Ser His Leu Ile Gln Phe Leu Val Phe Leu Gly Leu Met
20 25 30

Val Thr Tyr Ile Val Thr Ala Thr Gly Lys Leu Leu Ile Ile Val Leu
35 40 45

Ser Trp Ile Asp Gln Arg Leu His Ile Gln Met Tyr Phe Phe Leu Arg
50 55 60

Asn Phe Ser Phe Leu Glu Leu Leu Leu Val Thr Val Val Val Pro Lys
65 70 75 80

Met Leu Val Val Ile Leu Thr Gly Asp His Thr Ile Ser Phe Val Ser
85 90 95

Cys Ile Ile Gln Ser Tyr Leu Tyr Phe Phe Leu Gly Thr Thr Asp Phe
100 105 110

Phe Leu Leu Ala Val Met Ser Leu Asp Arg Tyr Leu Ala Ile Cys Arg
115 120 125

Pro Leu Arg Tyr Glu Thr Leu Met Asn Gly His Val Cys Ser Gln Leu
130 135 140

Val Leu Ala Ser Trp Leu Ala Gly Phe Leu Trp Val Leu Cys Pro Thr
145 150 155 160

Val Leu Met Ala Ser Leu Pro Phe Cys Gly Pro Asn Gly Ile Asp His
165 170 175

Phe Phe Arg Asp Ser Trp Pro Leu Leu Arg Leu Ser Cys Gly Asp Thr
180 185 190

His Leu Leu Lys Leu Val Ala Phe Met Leu Ser Thr Leu Val Leu Leu
195 200 205

Gly Ser Leu Ala Leu Thr Ser Val Ser Tyr Ala Cys Ile Leu Ala Thr
210 215 220

Val Leu Arg Ala Pro Thr Ala Ala Glu Arg Arg Lys Ala Phe Ser Thr
225 230 235 240

Cys Ala Ser His Leu Thr Val Val Val Ile Ile Tyr Gly Ser Ser Ile
245 250 255

Phe Leu Tyr Ile Arg Met Ser Glu Ala Gln Ser Lys Leu Leu Asn Lys

DOCID: <WO_____03089583A2_I_>

260 265 270

Gly Ala Ser Val Leu Ser Cys Ile Ile Thr Pro Leu Leu Asn Pro Phe
275 280 285

Ile Phe Thr Leu Arg Asn Asp Lys Val Gln Gln Ala Leu Arg Glu Ala
290 295 300

Leu Gly Trp Pro Arg Leu Thr Ala Val Met Lys Leu Arg Val Thr Ser
305 310 315 320

Gln Arg Lys

<210> 169
<211> 25
<212> DNA
<213> Homo sapiens

<400> 169
tgtgctcagc tggatagacc aacgc 25

<210> 170
<211> 30
<212> DNA
<213> Homo sapiens

<400> 170
ctgagaacag tggcaagaat gcaggcatag 30

<210> 171
<211> 450
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(450)
<223>

<400> 171
atg gac ctt ccc cat gtc cca gct ctg gac gcc cca ctc ttt gga gtc 48
Met Asp Leu Pro His Val Pro Ala Leu Asp Ala Pro Leu Phe Gly Val
1 5 10 15

ttc ctg gtg gtt tat gtg ctt act gtg ctg ggg aac ctc ctc atc ctg 96
Phe Leu Val Val Tyr Val Leu Thr Val Leu Gly Asn Leu Leu Ile Leu
20 25 30

ctg gtg atc agg gtg tac tct cac ctc cac acc ccc aag tac tac ttc 144
Leu Val Ile Arg Val Tyr Ser His Leu His Thr Pro Lys Tyr Tyr Phe
35 40 45

ctc acc aat ctg tcc ttc att gac ttg tgg ttc ttc act gtc atg gtg 192
Leu Thr Asn Leu Ser Phe Ile Asp Leu Trp Phe Phe Thr Val Met Val
50 55 60

ccc aaa atg ccg agg acc ttg ttg tcc ctg tgt ggc aag gct gtg tcc 240
Pro Lys Met Pro Arg Thr Leu Leu Ser Leu Cys Gly Lys Ala Val Ser
65 70 75 80

ttc cac agt tgt atg acc caa ctc tat ttc ttc tac ttc ctg ggg agc 288
Phe His Ser Cys Met Thr Gln Leu Tyr Phe Phe Tyr Phe Leu Gly Ser
85 90 95

acc gag tgt ttg ctc tac acg gtc atg tcc tat gat cgc tat aga gga 336
Thr Glu Cys Leu Leu Tyr Thr Val Met Ser Tyr Asp Arg Tyr Arg Gly
100 105 110

aat act cag cac ttc cca ggt agt gaa aac act ccc cac gaa gtg agc 384
Asn Thr Gln His Phe Pro Gly Ser Glu Asn Thr Pro His Glu Val Ser
115 120 125

DCID: <WO 03089583A2 I >

caa atg cta gtg gcc cgg ggg gca cac ggg ctc cca ctc atc atc ctg 432
Gln Met Leu Val Ala Arg Gly Ala His Gly Leu Pro Leu Ile Ile Leu
130 135 140

gca gat ctg agt ggg taa 450
Ala Asp Leu Ser Gly
145

<210> 172
<211> 149
<212> PRT
<213> Homo sapiens

<400> 172

Met Asp Leu Pro His Val Pro Ala Leu Asp Ala Pro Leu Phe Gly Val
1 5 10 15

Phe Leu Val Val Tyr Val Leu Thr Val Leu Gly Asn Leu Leu Ile Leu
20 25 30

Leu Val Ile Arg Val Tyr Ser His Leu His Thr Pro Lys Tyr Tyr Phe
35 40 45

Leu Thr Asn Leu Ser Phe Ile Asp Leu Trp Phe Phe Thr Val Met Val
50 55 60

Pro Lys Met Pro Arg Thr Leu Leu Ser Leu Cys Gly Lys Ala Val Ser
65 70 75 80

Phe His Ser Cys Met Thr Gln Leu Tyr Phe Phe Tyr Phe Leu Gly Ser
85 90 95

Thr Glu Cys Leu Leu Tyr Thr Val Met Ser Tyr Asp Arg Tyr Arg Gly
100 105 110

Asn Thr Gln His Phe Pro Gly Ser Glu Asn Thr Pro His Glu Val Ser
115 120 125

Gln Met Leu Val Ala Arg Gly Ala His Gly Leu Pro Leu Ile Ile Leu
130 135 140

Ala Asp Leu Ser Gly
145

<210> 173
<211> 23
<212> DNA
<213> Homo sapiens

<400> 173
agctctggac gccccactct ttg 23

<210> 174
<211> 27
<212> DNA
<213> Homo sapiens

<400> 174
acccactcag atctgccagg atgatga 27

<210> 175
<211> 936
<212> DNA
<213> Homo sapiens

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<220>
<221> CDS
<222> (1)..(936)
<223>

<400> 175

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atg tcc aac gcc agc ctc gtg aca gca ttc atc ctc aca ggc ctt ccc       48
Met Ser Asn Ala Ser Leu Val Thr Ala Phe Ile Leu Thr Gly Leu Pro
1               5                  10                  15

cat gcc cca ggg ctg gac gcc ctc ctc ttt gga atc ttc ctg gtg gtt       96
His Ala Pro Gly Leu Asp Ala Leu Leu Phe Gly Ile Phe Leu Val Val
            20                  25                  30

tac gtg ctc act gtg ctg ggg aac ctc ctc atc ctg ctg gtg atc agg      144
Tyr Val Leu Thr Val Leu Gly Asn Leu Leu Ile Leu Leu Val Ile Arg
        35                  40                  45

gtg gat tct cac ctc cac acc ccc atg tac tac ttc ctc acc aac ctg      192
Val Asp Ser His Leu His Thr Pro Met Tyr Tyr Phe Leu Thr Asn Leu
    50                  55                  60

tcc ttc att gac atg tgg ttc tcc act gtc acg gtg ccc aaa atg ctg      240
Ser Phe Ile Asp Met Trp Phe Ser Thr Val Thr Val Pro Lys Met Leu
65                  70                  75                  80

atg acc ttg gtg tcc cca agc ggc agg gct atc tcc ttc cac agc tgc      288
Met Thr Leu Val Ser Pro Ser Gly Arg Ala Ile Ser Phe His Ser Cys
                85                  90                  95

gtg gct cag ctc tat ttt ttc cac ttc ctg ggg agc acc gag tgt ttc      336
Val Ala Gln Leu Tyr Phe Phe His Phe Leu Gly Ser Thr Glu Cys Phe
            100                 105                 110

ctc tac aca gtc atg tcc tat gat cgc tac ttg gcc atc agt tac ccg      384
Leu Tyr Thr Val Met Ser Tyr Asp Arg Tyr Leu Ala Ile Ser Tyr Pro
        115                 120                 125

ctc agg tac acc agc atg atg agt ggg agc agg tgt gcc ctc ctg gcc      432
Leu Arg Tyr Thr Ser Met Met Ser Gly Ser Arg Cys Ala Leu Leu Ala
    130                 135                 140

acc ggc act tgg ctc agt ggc tct ctg cac tct gct gtc cag acc ata      480
Thr Gly Thr Trp Leu Ser Gly Ser Leu His Ser Ala Val Gln Thr Ile
145                 150                 155                 160

ttg act ttc cat ttg ccc tac tgt gga ccc aac cag atc cag cac tac      528
Leu Thr Phe His Leu Pro Tyr Cys Gly Pro Asn Gln Ile Gln His Tyr
                165                 170                 175

ttc tgt gac gca ccg ccc atc ctg aaa ctg gcc tgt gca gac acc tca      576
Phe Cys Asp Ala Pro Pro Ile Leu Lys Leu Ala Cys Ala Asp Thr Ser
            180                 185                 190

gcc aac gtg atg gtc atc ttt gtg gac att ggg ata gtg gcc tca ggc      624
Ala Asn Val Met Val Ile Phe Val Asp Ile Gly Ile Val Ala Ser Gly
        195                 200                 205

tgc ttt gtc ctg ata gtg ctg tcc tat gtg tcc atc gtc tgt tcc atc      672
Cys Phe Val Leu Ile Val Leu Ser Tyr Val Ser Ile Val Cys Ser Ile
    210                 215                 220

ctg cgg atc cgc acc tca gat ggg agg cgc aga gcc ttt cag acc tgt      720
Leu Arg Ile Arg Thr Ser Asp Gly Arg Arg Arg Ala Phe Gln Thr Cys
225                 230                 235                 240

gcc tcc cac tgt att gtg gtc ctt tgc ttc ttt gtt ccc tgt gtt gtc      768
Ala Ser His Cys Ile Val Val Leu Cys Phe Phe Val Pro Cys Val Val
                245                 250                 255

att tat ctg agg cca ggc tcc atg gat gcc atg gat gga gtt gtg gcc      816
Ile Tyr Leu Arg Pro Gly Ser Met Asp Ala Met Asp Gly Val Val Ala
            260                 265                 270

att ttc tac act gtg ctg acg ccc ctt ctc aac cct gtt gtg tac acc      864
Ile Phe Tyr Thr Val Leu Thr Pro Leu Leu Asn Pro Val Val Tyr Thr
        275                 280                 285
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OCID: <WO_____03089583A2 I >

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ctg aga aac aag gag gtg aag aaa gct gtg ttg aaa ctt aga gac aaa      912
Leu Arg Asn Lys Glu Val Lys Lys Ala Val Leu Lys Leu Arg Asp Lys
    290                 295                 300

gta gca cat cct cag agg aaa taa                                     936
Val Ala His Pro Gln Arg Lys
305                 310
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<210> 176
<211> 311
<212> PRT
<213> Homo sapiens

<400> 176

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Met Ser Asn Ala Ser Leu Val Thr Ala Phe Ile Leu Thr Gly Leu Pro
1               5                   10                  15

His Ala Pro Gly Leu Asp Ala Leu Leu Phe Gly Ile Phe Leu Val Val
            20                  25                  30

Tyr Val Leu Thr Val Leu Gly Asn Leu Leu Ile Leu Leu Val Ile Arg
        35                  40                  45

Val Asp Ser His Leu His Thr Pro Met Tyr Tyr Phe Leu Thr Asn Leu
    50                  55                  60

Ser Phe Ile Asp Met Trp Phe Ser Thr Val Thr Val Pro Lys Met Leu
65                  70                  75                  80

Met Thr Leu Val Ser Pro Ser Gly Arg Ala Ile Ser Phe His Ser Cys
                85                  90                  95

Val Ala Gln Leu Tyr Phe Phe His Phe Leu Gly Ser Thr Glu Cys Phe
            100                 105                 110

Leu Tyr Thr Val Met Ser Tyr Asp Arg Tyr Leu Ala Ile Ser Tyr Pro
        115                 120                 125

Leu Arg Tyr Thr Ser Met Met Ser Gly Ser Arg Cys Ala Leu Leu Ala
    130                 135                 140

Thr Gly Thr Trp Leu Ser Gly Ser Leu His Ser Ala Val Gln Thr Ile
145                 150                 155                 160

Leu Thr Phe His Leu Pro Tyr Cys Gly Pro Asn Gln Ile Gln His Tyr
                165                 170                 175

Phe Cys Asp Ala Pro Pro Ile Leu Lys Leu Ala Cys Ala Asp Thr Ser
            180                 185                 190

Ala Asn Val Met Val Ile Phe Val Asp Ile Gly Ile Val Ala Ser Gly
        195                 200                 205

Cys Phe Val Leu Ile Val Leu Ser Tyr Val Ser Ile Val Cys Ser Ile
    210                 215                 220

Leu Arg Ile Arg Thr Ser Asp Gly Arg Arg Arg Ala Phe Gln Thr Cys
225                 230                 235                 240

Ala Ser His Cys Ile Val Val Leu Cys Phe Phe Val Pro Cys Val Val
                245                 250                 255
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DOCID: <WO_ ... 03089583A2_I_>

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Ile Tyr Leu Arg Pro Gly Ser Met Asp Ala Met Asp Gly Val Val Ala
            260                 265                 270

Ile Phe Tyr Thr Val Leu Thr Pro Leu Leu Asn Pro Val Val Tyr Thr
        275                 280                 285

Leu Arg Asn Lys Glu Val Lys Lys Ala Val Leu Lys Leu Arg Asp Lys
    290                 295                 300

Val Ala His Pro Gln Arg Lys
305                 310
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<210> 177
<211> 29
<212> DNA
<213> Homo sapiens

<400> 177
caaccagatc cagcactact tctgtgacg 29

<210> 178
<211> 33
<212> DNA
<213> Homo sapiens

<400> 178
ttatttcctc tgaggatgtg ctactttgtc tct 33

<210> 179
<211> 50
<212> DNA
<213> Homo sapiens

<400> 179
taggagaagc cctttaaaag caggcaatag taaggacatc agtaacaata 50

<210> 180
<211> 50
<212> DNA
<213> Homo sapiens

<400> 180
gctgggtgct ctttatatcc ccagagggag agagaccaag ggtgagaaga 50

<210> 181
<211> 921
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(921)
<223>

<400> 181

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atg gtg act gag ttt ctt ctt ctc ggc ttc tcc cac ctg gcc gac ctc      48
Met Val Thr Glu Phe Leu Leu Leu Gly Phe Ser His Leu Ala Asp Leu
1               5                  10                  15

cag ggc ttg ctc ttc tct gtc ttt ctc act atc tac ctg ctg acc gtg      96
Gln Gly Leu Leu Phe Ser Val Phe Leu Thr Ile Tyr Leu Leu Thr Val
            20                  25                  30

gca ggc aat ttc ctc att gtg gtg ctg gtc tcc act gat gct gcc ctc     144
Ala Gly Asn Phe Leu Ile Val Val Leu Val Ser Thr Asp Ala Ala Leu
        35                  40                  45

cag tcc cct atg tac ttc ttc ctg cgc acc ctc tcg gcc ttg gag att     192
Gln Ser Pro Met Tyr Phe Phe Leu Arg Thr Leu Ser Ala Leu Glu Ile
    50                  55                  60
```


IOCID: <WO_____03089583A2_I_>

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ggc tat acg tct gtc acg gtc ccc ctg cta ctt cac cac ctc ctt act      240
Gly Tyr Thr Ser Val Thr Val Pro Leu Leu Leu His His Leu Leu Thr
65                  70                  75                  80

ggc cgg cgc cac atc tct cgc tct gga tgt gct ctc cag atg ttc ttc      288
Gly Arg Arg His Ile Ser Arg Ser Gly Cys Ala Leu Gln Met Phe Phe
                85                  90                  95

ttc ctc ttc ttt ggc gcc acg gag tgc tgc ctc ctg gca gcc atg gcc      336
Phe Leu Phe Phe Gly Ala Thr Glu Cys Cys Leu Leu Ala Ala Met Ala
            100                 105                 110

tat gac cgc tat gca gcc atc tgt gaa ccc ctc cgc tac cca ctg ctg      384
Tyr Asp Arg Tyr Ala Ala Ile Cys Glu Pro Leu Arg Tyr Pro Leu Leu
        115                 120                 125

ctg agc cac cgg gtg tgt cta cag cta gct ggg tcg gcg tgg gcc tgt      432
Leu Ser His Arg Val Cys Leu Gln Leu Ala Gly Ser Ala Trp Ala Cys
    130                 135                 140

ggg gtg ctg gtg ggg ctg ggc cac acc cct ttc atc ttc tct ttg ccc      480
Gly Val Leu Val Gly Leu Gly His Thr Pro Phe Ile Phe Ser Leu Pro
145                 150                 155                 160

ttc tgc ggc ccc aat acc atc ccg cag ttc ttc tgt gag atc cag cct      528
Phe Cys Gly Pro Asn Thr Ile Pro Gln Phe Phe Cys Glu Ile Gln Pro
                165                 170                 175

gtc ctg cag ctg gta tgt gga gac acc tcg ctt aat gaa ctg cag att      576
Val Leu Gln Leu Val Cys Gly Asp Thr Ser Leu Asn Glu Leu Gln Ile
            180                 185                 190

atc ctg gca aca gcc ctc ctc atc ctc tgc ccc ttt ggc ctc atc ctg      624
Ile Leu Ala Thr Ala Leu Leu Ile Leu Cys Pro Phe Gly Leu Ile Leu
        195                 200                 205

ggc tcc tac ggg cgt atc ctc gtt acc atc ttc cgg atc cca tct gtt      672
Gly Ser Tyr Gly Arg Ile Leu Val Thr Ile Phe Arg Ile Pro Ser Val
    210                 215                 220

gcg ggc cgc cgc aag gcc ttc tcc acc tgc tcc tcc cac ctg atc gtg      720
Ala Gly Arg Arg Lys Ala Phe Ser Thr Cys Ser Ser His Leu Ile Val
225                 230                 235                 240

gtc tcc ctc ttc tat ggc acc gca ctc ttt atc tat att cgc cct aag      768
Val Ser Leu Phe Tyr Gly Thr Ala Leu Phe Ile Tyr Ile Arg Pro Lys
                245                 250                 255

gcc agc tac gat ccg gcc act gac cct ctg gtg tcc ctc ttc tat gct      816
Ala Ser Tyr Asp Pro Ala Thr Asp Pro Leu Val Ser Leu Phe Tyr Ala
            260                 265                 270

gtg gtc acc ccc atc ctc aac ccc atc atc tac agc ctg cgg aac aca      864
Val Val Thr Pro Ile Leu Asn Pro Ile Ile Tyr Ser Leu Arg Asn Thr
        275                 280                 285

gag gtc aaa gct gcc cta aag aga acc atc cag aaa acg gtg cct atg      912
Glu Val Lys Ala Ala Leu Lys Arg Thr Ile Gln Lys Thr Val Pro Met
    290                 295                 300

gag att tga                                                         921
Glu Ile
305
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<210> 182
<211> 306
<212> PRT
<213> Homo sapiens

<400> 182

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Met Val Thr Glu Phe Leu Leu Leu Gly Phe Ser His Leu Ala Asp Leu
1               5                   10                  15

Gln Gly Leu Leu Phe Ser Val Phe Leu Thr Ile Tyr Leu Leu Thr Val
            20                  25                  30
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DOCID: <WO ____0308958 3A2 I >

Ala Gly Asn Phe Leu Ile Val Val Leu Val Ser Thr Asp Ala Ala Leu
35 40 45

Gln Ser Pro Met Tyr Phe Phe Leu Arg Thr Leu Ser Ala Leu Glu Ile
50 55 60

Gly Tyr Thr Ser Val Thr Val Pro Leu Leu Leu His His Leu Leu Thr
65 70 75 80

Gly Arg Arg His Ile Ser Arg Ser Gly Cys Ala Leu Gln Met Phe Phe
85 90 95

Phe Leu Phe Phe Gly Ala Thr Glu Cys Cys Leu Leu Ala Ala Met Ala
100 105 110

Tyr Asp Arg Tyr Ala Ala Ile Cys Glu Pro Leu Arg Tyr Pro Leu Leu
115 120 125

Leu Ser His Arg Val Cys Leu Gln Leu Ala Gly Ser Ala Trp Ala Cys
130 135 140

Gly Val Leu Val Gly Leu Gly His Thr Pro Phe Ile Phe Ser Leu Pro
145 150 155 160

Phe Cys Gly Pro Asn Thr Ile Pro Gln Phe Phe Cys Glu Ile Gln Pro
165 170 175

Val Leu Gln Leu Val Cys Gly Asp Thr Ser Leu Asn Glu Leu Gln Ile
180 185 190

Ile Leu Ala Thr Ala Leu Leu Ile Leu Cys Pro Phe Gly Leu Ile Leu
195 200 205

Gly Ser Tyr Gly Arg Ile Leu Val Thr Ile Phe Arg Ile Pro Ser Val
210 215 220

Ala Gly Arg Arg Lys Ala Phe Ser Thr Cys Ser Ser His Leu Ile Val
225 230 235 240

Val Ser Leu Phe Tyr Gly Thr Ala Leu Phe Ile Tyr Ile Arg Pro Lys
245 250 255

Ala Ser Tyr Asp Pro Ala Thr Asp Pro Leu Val Ser Leu Phe Tyr Ala
260 265 270

Val Val Thr Pro Ile Leu Asn Pro Ile Ile Tyr Ser Leu Arg Asn Thr
275 280 285

Glu Val Lys Ala Ala Leu Lys Arg Thr Ile Gln Lys Thr Val Pro Met
290 295 300

Glu Ile
305

<210> 183
<211> 20
<212> DNA
<213> Homo sapiens

XCID: <WO ___ 03089583A2 I >

<400> 183
ctcggcttct cccacctggc 20

<210> 184
<211> 23
<212> DNA
<213> Homo sapiens

<400> 184
ggcgccaaag aagaggaaga aga 23

<210> 185
<211> 897
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(897)
<223>

<400> 185
atg ggt cga gga aac agc act gaa gtg act gaa ttc cat ctt ctg gga 48
Met Gly Arg Gly Asn Ser Thr Glu Val Thr Glu Phe His Leu Leu Gly
1 5 10 15

ttt ggt gtc caa cac gaa ttt cag cat gtc ctt ttc att gta ctt ctt 96
Phe Gly Val Gln His Glu Phe Gln His Val Leu Phe Ile Val Leu Leu
20 25 30

ctt atc tat gtg acc tcc ctg ata gga aat att gga atg atc tta ctc 144
Leu Ile Tyr Val Thr Ser Leu Ile Gly Asn Ile Gly Met Ile Leu Leu
35 40 45

atc aag acc gat tcc aga ctt caa aca ccc atg tac ttt ttt cca caa 192
Ile Lys Thr Asp Ser Arg Leu Gln Thr Pro Met Tyr Phe Phe Pro Gln
50 55 60

cat ttg gct ttt gtt gat atc tgt tat act tct gct atc act ccc aag 240
His Leu Ala Phe Val Asp Ile Cys Tyr Thr Ser Ala Ile Thr Pro Lys
65 70 75 80

atg ctc caa agc ttc aca gaa gaa aat aat ttg ata aca ttt cgg ggc 288
Met Leu Gln Ser Phe Thr Glu Glu Asn Asn Leu Ile Thr Phe Arg Gly
85 90 95

tgt gtg ata caa ttc tta gtt tat gca aca ttt gca acc agt gac tgt 336
Cys Val Ile Gln Phe Leu Val Tyr Ala Thr Phe Ala Thr Ser Asp Cys
100 105 110

tac ctc cta gct att atg gca atg gat tgt tat gtt gcc atc tgt aag 384
Tyr Leu Leu Ala Ile Met Ala Met Asp Cys Tyr Val Ala Ile Cys Lys
115 120 125

ccc ctt cgc tat ccc atg atc atg tcc caa aca gtc tac atc caa ctc 432
Pro Leu Arg Tyr Pro Met Ile Met Ser Gln Thr Val Tyr Ile Gln Leu
130 135 140

gta gct ggc tca tat att ata ggc tca ata aat gcc tct gta cat aca 480
Val Ala Gly Ser Tyr Ile Ile Gly Ser Ile Asn Ala Ser Val His Thr
145 150 155 160

ggt ttt aca ttt tca ctg tcc ttc tgc aag tct aat aaa atc aat cac 528
Gly Phe Thr Phe Ser Leu Ser Phe Cys Lys Ser Asn Lys Ile Asn His
165 170 175

ttt ttc tgt gat ggt ctc cca att ctt gcc ctt tca tgc tcc aac att 576
Phe Phe Cys Asp Gly Leu Pro Ile Leu Ala Leu Ser Cys Ser Asn Ile
180 185 190

gac atc aac atc att cta gat gtt gtc ttt gtg gga ttt gac ttg atg 624
Asp Ile Asn Ile Ile Leu Asp Val Val Phe Val Gly Phe Asp Leu Met
195 200 205

ttc act gag ttg gtc atc atc ttt tcc tac atc tac att atg gtc acc 672
Phe Thr Glu Leu Val Ile Ile Phe Ser Tyr Ile Tyr Ile Met Val Thr
210 215 220

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atc ctg aag atg tct tct act gct ggg agg aaa aaa tcc ttc tcc aca      720
Ile Leu Lys Met Ser Ser Thr Ala Gly Arg Lys Lys Ser Phe Ser Thr
225                 230                 235                 240

tgt gcc tcc cac ctg aca gca gta acc att ttc tat ggg aca ctc tct      768
Cys Ala Ser His Leu Thr Ala Val Thr Ile Phe Tyr Gly Thr Leu Ser
                245                 250                 255

tac atg tac tta cag cct cag tct aat aat tct cag gag aat atg aaa      816
Tyr Met Tyr Leu Gln Pro Gln Ser Asn Asn Ser Gln Glu Asn Met Lys
            260                 265                 270

gta gcc tct ata ttt tat ggc act gtt att ccc atg ttg aat cct tta      864
Val Ala Ser Ile Phe Tyr Gly Thr Val Ile Pro Met Leu Asn Pro Leu
        275                 280                 285

atc tat agc ttg aga aat aag gaa gga aaa taa                          897
Ile Tyr Ser Leu Arg Asn Lys Glu Gly Lys
    290                 295
```

<210> 186
<211> 298
<212> PRT
<213> Homo sapiens

<400> 186

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Met Gly Arg Gly Asn Ser Thr Glu Val Thr Glu Phe His Leu Leu Gly
1               5                   10                  15

Phe Gly Val Gln His Glu Phe Gln His Val Leu Phe Ile Val Leu Leu
            20                  25                  30

Leu Ile Tyr Val Thr Ser Leu Ile Gly Asn Ile Gly Met Ile Leu Leu
        35                  40                  45

Ile Lys Thr Asp Ser Arg Leu Gln Thr Pro Met Tyr Phe Phe Pro Gln
    50                  55                  60

His Leu Ala Phe Val Asp Ile Cys Tyr Thr Ser Ala Ile Thr Pro Lys
65                  70                  75                  80

Met Leu Gln Ser Phe Thr Glu Glu Asn Asn Leu Ile Thr Phe Arg Gly
                85                  90                  95

Cys Val Ile Gln Phe Leu Val Tyr Ala Thr Phe Ala Thr Ser Asp Cys
            100                 105                 110

Tyr Leu Leu Ala Ile Met Ala Met Asp Cys Tyr Val Ala Ile Cys Lys
        115                 120                 125

Pro Leu Arg Tyr Pro Met Ile Met Ser Gln Thr Val Tyr Ile Gln Leu
    130                 135                 140

Val Ala Gly Ser Tyr Ile Ile Gly Ser Ile Asn Ala Ser Val His Thr
145                 150                 155                 160

Gly Phe Thr Phe Ser Leu Ser Phe Cys Lys Ser Asn Lys Ile Asn His
                165                 170                 175

Phe Phe Cys Asp Gly Leu Pro Ile Leu Ala Leu Ser Cys Ser Asn Ile
            180                 185                 190

Asp Ile Asn Ile Ile Leu Asp Val Val Phe Val Gly Phe Asp Leu Met
        195                 200                 205
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OCID: <WO_____03089583A2 I >

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Phe Thr Glu Leu Val Ile Ile Phe Ser Tyr Ile Tyr Ile Met Val Thr
    210                 215                 220

Ile Leu Lys Met Ser Ser Thr Ala Gly Arg Lys Lys Ser Phe Ser Thr
225                 230                 235                 240

Cys Ala Ser His Leu Thr Ala Val Thr Ile Phe Tyr Gly Thr Leu Ser
                245                 250                 255

Tyr Met Tyr Leu Gln Pro Gln Ser Asn Asn Ser Gln Glu Asn Met Lys
            260                 265                 270

Val Ala Ser Ile Phe Tyr Gly Thr Val Ile Pro Met Leu Asn Pro Leu
        275                 280                 285

Ile Tyr Ser Leu Arg Asn Lys Glu Gly Lys
    290                 295
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<210> 187
<211> 930
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(930)
<223>

<400> 187

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atg aca cta gga aac agc act gaa gtc act gaa ttc tat ctt ctg gga      48
Met Thr Leu Gly Asn Ser Thr Glu Val Thr Glu Phe Tyr Leu Leu Gly
1               5                   10                  15

ttt ggt gcc cag cat gag ttt tgg tgt atc ctc ttc att gta ttc ctt      96
Phe Gly Ala Gln His Glu Phe Trp Cys Ile Leu Phe Ile Val Phe Leu
            20                  25                  30

ctc atc tat gtg acc tcc ata atg ggt aat agt gga ata atc tta ctc     144
Leu Ile Tyr Val Thr Ser Ile Met Gly Asn Ser Gly Ile Ile Leu Leu
        35                  40                  45

atc aac aca gat tcc aga ttt caa aca ctc acg tac ttt ttt cta caa     192
Ile Asn Thr Asp Ser Arg Phe Gln Thr Leu Thr Tyr Phe Phe Leu Gln
    50                  55                  60

cat ttg gct ttt gtt gat atc tgt tac act tct gct atc act ccc aag     240
His Leu Ala Phe Val Asp Ile Cys Tyr Thr Ser Ala Ile Thr Pro Lys
65                  70                  75                  80

atg ctc caa agc ttc aca gaa gaa aag aat ttg atg tta ttt cag ggc     288
Met Leu Gln Ser Phe Thr Glu Glu Lys Asn Leu Met Leu Phe Gln Gly
                85                  90                  95

tgt gtg ata caa ttc tta gtt tat gca aca ttt gca acc agt gac tgt     336
Cys Val Ile Gln Phe Leu Val Tyr Ala Thr Phe Ala Thr Ser Asp Cys
            100                 105                 110

tat ctc ctg gct atg atg gca gtg gat cct tat gtt gcc atc tgt aag     384
Tyr Leu Leu Ala Met Met Ala Val Asp Pro Tyr Val Ala Ile Cys Lys
        115                 120                 125

ccc ctt cac tat act gta atc atg tcc cga aca gtc tgc atc cgt ttg     432
Pro Leu His Tyr Thr Val Ile Met Ser Arg Thr Val Cys Ile Arg Leu
    130                 135                 140

gta gct ggt tca tac atc atg ggc tca ata aat gcc tct gta caa aca     480
Val Ala Gly Ser Tyr Ile Met Gly Ser Ile Asn Ala Ser Val Gln Thr
145                 150                 155                 160

ggt ttt aca tgt tca ctg tcc ttc tgc aag tcc aat agc atc aat cac     528
Gly Phe Thr Cys Ser Leu Ser Phe Cys Lys Ser Asn Ser Ile Asn His
```


DOCID: <WO_____03089583A2_I_>

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                165                 170                 175

ttt ttc tgt gat gtt ccc cct att ctt gct ctt tca tgc tcc aat gtt      576
Phe Phe Cys Asp Val Pro Pro Ile Leu Ala Leu Ser Cys Ser Asn Val
            180                 185                 190

gac atc aac atc atg cta ctt gtt gtc ttt gtg gga tct aac ttg ata      624
Asp Ile Asn Ile Met Leu Leu Val Val Phe Val Gly Ser Asn Leu Ile
        195                 200                 205

ttc act ggg ttg gtc gtc atc ttt tcc tac atc tac atc atg gcc acc      672
Phe Thr Gly Leu Val Val Ile Phe Ser Tyr Ile Tyr Ile Met Ala Thr
    210                 215                 220

atc ctg aaa atg tct tct agt gca gga agg aaa aaa tcc ttc tca aca      720
Ile Leu Lys Met Ser Ser Ser Ala Gly Arg Lys Lys Ser Phe Ser Thr
225                 230                 235                 240

tgt gct tcc cac ctg acc gca gtc acc att ttc tat ggg aca ctc tct      768
Cys Ala Ser His Leu Thr Ala Val Thr Ile Phe Tyr Gly Thr Leu Ser
                245                 250                 255

tac atg tat ttg cag tct cat tct aat aat tcc cag gaa aat atg aaa      816
Tyr Met Tyr Leu Gln Ser His Ser Asn Asn Ser Gln Glu Asn Met Lys
            260                 265                 270

gtg gcc ttt ata ttt tat ggc aca gtt att ccc atg tta aat cct tta      864
Val Ala Phe Ile Phe Tyr Gly Thr Val Ile Pro Met Leu Asn Pro Leu
        275                 280                 285

atc tat agc ttg aga aat aag gaa gta aaa gaa gct tta aaa gtg ata      912
Ile Tyr Ser Leu Arg Asn Lys Glu Val Lys Glu Ala Leu Lys Val Ile
    290                 295                 300

ggg aaa aag tta ttt taa                                             930
Gly Lys Lys Leu Phe
305
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<210> 188
<211> 309
<212> PRT
<213> Homo sapiens

<400> 188

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Met Thr Leu Gly Asn Ser Thr Glu Val Thr Glu Phe Tyr Leu Leu Gly
1               5                   10                  15

Phe Gly Ala Gln His Glu Phe Trp Cys Ile Leu Phe Ile Val Phe Leu
            20                  25                  30

Leu Ile Tyr Val Thr Ser Ile Met Gly Asn Ser Gly Ile Ile Leu Leu
        35                  40                  45

Ile Asn Thr Asp Ser Arg Phe Gln Thr Leu Thr Tyr Phe Phe Leu Gln
    50                  55                  60

His Leu Ala Phe Val Asp Ile Cys Tyr Thr Ser Ala Ile Thr Pro Lys
65                  70                  75                  80

Met Leu Gln Ser Phe Thr Glu Glu Lys Asn Leu Met Leu Phe Gln Gly
                85                  90                  95

Cys Val Ile Gln Phe Leu Val Tyr Ala Thr Phe Ala Thr Ser Asp Cys
            100                 105                 110

Tyr Leu Leu Ala Met Met Ala Val Asp Pro Tyr Val Ala Ile Cys Lys
        115                 120                 125

Pro Leu His Tyr Thr Val Ile Met Ser Arg Thr Val Cys Ile Arg Leu
```


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130                 135                 140

Val Ala Gly Ser Tyr Ile Met Gly Ser Ile Asn Ala Ser Val Gln Thr
145                 150                 155                 160

Gly Phe Thr Cys Ser Leu Ser Phe Cys Lys Ser Asn Ser Ile Asn His
                165                 170                 175

Phe Phe Cys Asp Val Pro Pro Ile Leu Ala Leu Ser Cys Ser Asn Val
            180                 185                 190

Asp Ile Asn Ile Met Leu Leu Val Val Phe Val Gly Ser Asn Leu Ile
        195                 200                 205

Phe Thr Gly Leu Val Val Ile Phe Ser Tyr Ile Tyr Ile Met Ala Thr
    210                 215                 220

Ile Leu Lys Met Ser Ser Ser Ala Gly Arg Lys Lys Ser Phe Ser Thr
225                 230                 235                 240

Cys Ala Ser His Leu Thr Ala Val Thr Ile Phe Tyr Gly Thr Leu Ser
                245                 250                 255

Tyr Met Tyr Leu Gln Ser His Ser Asn Asn Ser Gln Glu Asn Met Lys
            260                 265                 270

Val Ala Phe Ile Phe Tyr Gly Thr Val Ile Pro Met Leu Asn Pro Leu
        275                 280                 285

Ile Tyr Ser Leu Arg Asn Lys Glu Val Lys Glu Ala Leu Lys Val Ile
    290                 295                 300

Gly Lys Lys Leu Phe
305
```

<210> 189
<211> 522
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(522)
<223>

<400> 189

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atg ctc caa agc ttc acg gaa gaa aag aat ttg ata tca ttt tgg ggc      48
Met Leu Gln Ser Phe Thr Glu Glu Lys Asn Leu Ile Ser Phe Trp Gly
-1              5                  10                  15

tgc atg ata caa tta ttg gtt tat gca aca ttt gca acc agt gac tgt      96
Cys Met Ile Gln Leu Leu Val Tyr Ala Thr Phe Ala Thr Ser Asp Cys
            20                  25                  30

tat ctc ctg gct atg ata gca gtg gac cat tat gtt gca atc tgt aag     144
Tyr Leu Leu Ala Met Ile Ala Val Asp His Tyr Val Ala Ile Cys Lys
        35                  40                  45

ccc ctt cac tat acc gta atc acg tcc caa aca gtc tgc atc cat ttg     192
Pro Leu His Tyr Thr Val Ile Thr Ser Gln Thr Val Cys Ile His Leu
    50                  55                  60

gta gct ggt tca tac atc atg ggc tca ata aat gcc tct gta cat aca     240
Val Ala Gly Ser Tyr Ile Met Gly Ser Ile Asn Ala Ser Val His Thr
65                  70                  75                  80

ggt ttt gca ttt tca ctg tct ttc tgc aag tcc aat aac atc aac cac     288
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DOCID: <WO_____03089583A2_I_>

```
Gly Phe Ala Phe Ser Leu Ser Phe Cys Lys Ser Asn Asn Ile Asn His
                85                  90                  95

ttt ttc tgt gat ggt ccc cca att ctt gcc ctt tca tgc tcc aat att      336
Phe Phe Cys Asp Gly Pro Pro Ile Leu Ala Leu Ser Cys Ser Asn Ile
            100                 105                 110

gac atc aac atc atg cta ctt gtt gtc ttt gtg gga ttt aac ttg atg      384
Asp Ile Asn Ile Met Leu Leu Val Val Phe Val Gly Phe Asn Leu Met
        115                 120                 125

ttc act ggg ttg gag aat atg aaa gtg gcc tct ata ttt tat ggc act      432
Phe Thr Gly Leu Glu Asn Met Lys Val Ala Ser Ile Phe Tyr Gly Thr
    130                 135                 140

gtt att ccc atg ttg aat cct tta atc tat agc ttg aga aat aag gaa      480
Val Ile Pro Met Leu Asn Pro Leu Ile Tyr Ser Leu Arg Asn Lys Glu
145                 150                 155                 160

gta aaa gaa gct tta aaa ttg ata ggg aaa aag ttc ttt taa              522
Val Lys Glu Ala Leu Lys Leu Ile Gly Lys Lys Phe Phe
                165                 170
```

<210> 190
<211> 173
<212> PRT
<213> Homo sapiens

<400> 190

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Met Leu Gln Ser Phe Thr Glu Glu Lys Asn Leu Ile Ser Phe Trp Gly
1               5                   10                  15

Cys Met Ile Gln Leu Leu Val Tyr Ala Thr Phe Ala Thr Ser Asp Cys
            20                  25                  30

Tyr Leu Leu Ala Met Ile Ala Val Asp His Tyr Val Ala Ile Cys Lys
        35                  40                  45

Pro Leu His Tyr Thr Val Ile Thr Ser Gln Thr Val Cys Ile His Leu
    50                  55                  60

Val Ala Gly Ser Tyr Ile Met Gly Ser Ile Asn Ala Ser Val His Thr
65                  70                  75                  80

Gly Phe Ala Phe Ser Leu Ser Phe Cys Lys Ser Asn Asn Ile Asn His
                85                  90                  95

Phe Phe Cys Asp Gly Pro Pro Ile Leu Ala Leu Ser Cys Ser Asn Ile
            100                 105                 110

Asp Ile Asn Ile Met Leu Leu Val Val Phe Val Gly Phe Asn Leu Met
        115                 120                 125

Phe Thr Gly Leu Glu Asn Met Lys Val Ala Ser Ile Phe Tyr Gly Thr
    130                 135                 140

Val Ile Pro Met Leu Asn Pro Leu Ile Tyr Ser Leu Arg Asn Lys Glu
145                 150                 155                 160

Val Lys Glu Ala Leu Lys Leu Ile Gly Lys Lys Phe Phe
                165                 170
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<210> 191
<211> 499
<212> DNA
<213> Homo sapiens

DCID: <WO .. 03089583A2 I >

<220>
<221> CDS
<222> (43)..(372)
<223>

<400> 191
cgttatgtgg ccttctgtaa cccactccat atccagggg tt atg tcc cag aga 54
Met Ser Gln Arg
1

ctc tgc att aag cta tta gtt agt tca tat gtc atg ggt ttc cta aat 102
Leu Cys Ile Lys Leu Leu Val Ser Ser Tyr Val Met Gly Phe Leu Asn
5 10 15 20

gcc tct ata aac ata agt ttc act ttc tca ttg aac ttc tgc aaa tcc 150
Ala Ser Ile Asn Ile Ser Phe Thr Phe Ser Leu Asn Phe Cys Lys Ser
25 30 35

aaa aca att aat cac ttt ttc tgt gat gaa cct cca att att gcc cta 198
Lys Thr Ile Asn His Phe Phe Cys Asp Glu Pro Pro Ile Ile Ala Leu
40 45 50

cca tgc tcc aat att gac ctc aac atc atg tta tta aca gta ttt gtg 246
Pro Cys Ser Asn Ile Asp Leu Asn Ile Met Leu Leu Thr Val Phe Val
55 60 65

gga tta aat ttg atg tgc act gtg atg gtg gtc atc att tcc tgc ata 294
Gly Leu Asn Leu Met Cys Thr Val Met Val Val Ile Ile Ser Cys Ile
70 75 80

tat gtc ctg gtt gcc atc ctg agg ata tct tct gct gca ggg aag aaa 342
Tyr Val Leu Val Ala Ile Leu Arg Ile Ser Ser Ala Ala Gly Lys Lys
85 90 95 100

aaa gtc tct cta cat gtg cct ccc acc tga cagcagtcac cattttctat 392
Lys Val Ser Leu His Val Pro Pro Thr
105

ggggttctct cttacatgta tctatgccat cgtattaatg agtctcaaaa acaagaaaaa 452

gtggcctctg tgttttatgg cattattatt cccatgttaa acccctt 499

<210> 192
<211> 109
<212> PRT
<213> Homo sapiens

<400> 192

Met Ser Gln Arg Leu Cys Ile Lys Leu Leu Val Ser Ser Tyr Val Met
1 5 10 15

Gly Phe Leu Asn Ala Ser Ile Asn Ile Ser Phe Thr Phe Ser Leu Asn
20 25 30

Phe Cys Lys Ser Lys Thr Ile Asn His Phe Phe Cys Asp Glu Pro Pro
35 40 45

Ile Ile Ala Leu Pro Cys Ser Asn Ile Asp Leu Asn Ile Met Leu Leu
50 55 60

Thr Val Phe Val Gly Leu Asn Leu Met Cys Thr Val Met Val Val Ile
65 70 75 80

Ile Ser Cys Ile Tyr Val Leu Val Ala Ile Leu Arg Ile Ser Ser Ala
85 90 95

Ala Gly Lys Lys Lys Val Ser Leu His Val Pro Pro Thr
100 105

DOCID: <WO_____03089583A2_I_>

<210> 193
<211> 681
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<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(681)
<223>

<400> 193

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atg gct tat gac cgc tac atg gca atc tcc aag ccc ctg ctt tat tcc       48
Met Ala Tyr Asp Arg Tyr Met Ala Ile Ser Lys Pro Leu Leu Tyr Ser
1               5                  10                  15

cgg gcc aca ttc cca gag tta tgt gcc agt ctt gtt gag gct tca cac       96
Arg Ala Thr Phe Pro Glu Leu Cys Ala Ser Leu Val Glu Ala Ser His
            20                  25                  30

ctt ggc ggc ttt gta aac tca acc atc atc acc agt gag aca cct acc      144
Leu Gly Gly Phe Val Asn Ser Thr Ile Ile Thr Ser Glu Thr Pro Thr
        35                  40                  45

ttg agc ttc tgt ggc agc aat atc att gat gat ttc ttc tgt gat ctg      192
Leu Ser Phe Cys Gly Ser Asn Ile Ile Asp Asp Phe Phe Cys Asp Leu
    50                  55                  60

ccc cca ctt gta aag ttg gtg tgt gat gtg aag gag cgc tac cag gct      240
Pro Pro Leu Val Lys Leu Val Cys Asp Val Lys Glu Arg Tyr Gln Ala
65                  70                  75                  80

gtg ctg cat ttt atg ctt gcc tcc aat cat cac tcc cac tgc act tat      288
Val Leu His Phe Met Leu Ala Ser Asn His His Ser His Cys Thr Tyr
                85                  90                  95

tct tgc gtc cat ctc ttc atc att gca gcc atc tcg aag atc cgt tcc      336
Ser Cys Val His Leu Phe Ile Ile Ala Ala Ile Ser Lys Ile Arg Ser
            100                 105                 110

att aag ggc cgc ctc cag gtc ttc tcc act tgt ggg tct ccc ctg acg      384
Ile Lys Gly Arg Leu Gln Val Phe Ser Thr Cys Gly Ser Pro Leu Thr
        115                 120                 125

gct ctc acc ttg tac tat ggt gca atc ttc ttt att tac tcc caa cca      432
Ala Leu Thr Leu Tyr Tyr Gly Ala Ile Phe Phe Ile Tyr Ser Gln Pro
    130                 135                 140

aga act agc tat gcc tta aaa atg gat aaa ttg ggg tca gtg ttc tat      480
Arg Thr Ser Tyr Ala Leu Lys Met Asp Lys Leu Gly Ser Val Phe Tyr
145                 150                 155                 160

act gtg gtg att cca atg cta aac ccc ttg atc tat agc tta aga aat      528
Thr Val Val Ile Pro Met Leu Asn Pro Leu Ile Tyr Ser Leu Arg Asn
                165                 170                 175

aag gat gtc aaa gat gcc ttg aag aaa atg tta gat aga ctt cag ttt      576
Lys Asp Val Lys Asp Ala Leu Lys Lys Met Leu Asp Arg Leu Gln Phe
            180                 185                 190

ctt aaa gaa aaa tat tgt aga tat ggg ctg gcc tgt agt gag cgc tac      624
Leu Lys Glu Lys Tyr Cys Arg Tyr Gly Leu Ala Cys Ser Glu Arg Tyr
        195                 200                 205

ctc ctg gct gcc atg ggt tat gac tgc tat gag gca atc tcc aag ccc      672
Leu Leu Ala Ala Met Gly Tyr Asp Cys Tyr Glu Ala Ile Ser Lys Pro
    210                 215                 220

ctg ctt taa                                                         681
Leu Leu
225
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<210> 194
<211> 226
<212> PRT
<213> Homo sapiens

<400> 194

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Met Ala Tyr Asp Arg Tyr Met Ala Ile Ser Lys Pro Leu Leu Tyr Ser
1 5 10 15

Arg Ala Thr Phe Pro Glu Leu Cys Ala Ser Leu Val Glu Ala Ser His
20 25 30

Leu Gly Gly Phe Val Asn Ser Thr Ile Ile Thr Ser Glu Thr Pro Thr
35 40 45

Leu Ser Phe Cys Gly Ser Asn Ile Ile Asp Asp Phe Phe Cys Asp Leu
50 55 60

Pro Pro Leu Val Lys Leu Val Cys Asp Val Lys Glu Arg Tyr Gln Ala
65 70 75 80

Val Leu His Phe Met Leu Ala Ser Asn His His Ser His Cys Thr Tyr
85 90 95

Ser Cys Val His Leu Phe Ile Ile Ala Ala Ile Ser Lys Ile Arg Ser
100 105 110

Ile Lys Gly Arg Leu Gln Val Phe Ser Thr Cys Gly Ser Pro Leu Thr
115 120 125

Ala Leu Thr Leu Tyr Tyr Gly Ala Ile Phe Phe Ile Tyr Ser Gln Pro
130 135 140

Arg Thr Ser Tyr Ala Leu Lys Met Asp Lys Leu Gly Ser Val Phe Tyr
145 150 155 160

Thr Val Val Ile Pro Met Leu Asn Pro Leu Ile Tyr Ser Leu Arg Asn
165 170 175

Lys Asp Val Lys Asp Ala Leu Lys Lys Met Leu Asp Arg Leu Gln Phe
180 185 190

Leu Lys Glu Lys Tyr Cys Arg Tyr Gly Leu Ala Cys Ser Glu Arg Tyr
195 200 205

Leu Leu Ala Ala Met Gly Tyr Asp Cys Tyr Glu Ala Ile Ser Lys Pro
210 215 220

Leu Leu
225

<210> 195
<211> 1095
<212> DNA
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<220>
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<223>

<400> 195
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Met Ala Ser Glu Thr Phe Asn Thr Glu Asp Pro Ala Gly Leu Met His
1 5 10 15

tcg gat gcc ggc acc agc tgc ccc gtc ctt tgc aca tgc cgt aac cag 96
Ser Asp Ala Gly Thr Ser Cys Pro Val Leu Cys Thr Cys Arg Asn Gln
20 25 30

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gtg gtg gat tgt agc agc cag cgg cta ttc tcc gtg ccc cca gac ctg      144
Val Val Asp Cys Ser Ser Gln Arg Leu Phe Ser Val Pro Pro Asp Leu
        35                  40                  45

cca atg gac acc cga aac ctc agc ctg gcc cac aac cgc atc aca gca      192
Pro Met Asp Thr Arg Asn Leu Ser Leu Ala His Asn Arg Ile Thr Ala
    50                  55                  60

gtg ccg cct ggc tac ctc aca tgc tac atg gag ctc cag gtg ctg gat      240
Val Pro Pro Gly Tyr Leu Thr Cys Tyr Met Glu Leu Gln Val Leu Asp
65                  70                  75                  80

ttg cac aac aac tcc tta atg gag ctg ccc cgg ggc ctc ttc ctc cat      288
Leu His Asn Asn Ser Leu Met Glu Leu Pro Arg Gly Leu Phe Leu His
                85                  90                  95

gcc aag cgc ttg gca cac ttg gac ctg agc tac aac aat ttc agc cat      336
Ala Lys Arg Leu Ala His Leu Asp Leu Ser Tyr Asn Asn Phe Ser His
            100                 105                 110

gtg cca gcc gac atg ttc cag gag gcc cat ggg cta gtc cac atc gac      384
Val Pro Ala Asp Met Phe Gln Glu Ala His Gly Leu Val His Ile Asp
        115                 120                 125

ctg agc cac aac ccc tgg ctg cgg agg gtg cat ccc cag gcc ttt cag      432
Leu Ser His Asn Pro Trp Leu Arg Arg Val His Pro Gln Ala Phe Gln
    130                 135                 140

ggc ctc atg cag ctc cga gac ctg gac ctc agt tat ggg ggc ctg gcc      480
Gly Leu Met Gln Leu Arg Asp Leu Asp Leu Ser Tyr Gly Gly Leu Ala
145                 150                 155                 160

ttc ctc agc ctg gag gct ctt gag ggc cta ccg ggg ctg gtg acc ctg      528
Phe Leu Ser Leu Glu Ala Leu Glu Gly Leu Pro Gly Leu Val Thr Leu
                165                 170                 175

cag atc ggt ggc aat ccc tgg gtg tgt ggc tgc acc atg gaa ccc ctg      576
Gln Ile Gly Gly Asn Pro Trp Val Cys Gly Cys Thr Met Glu Pro Leu
            180                 185                 190

ctg aag tgg ctg cga aac cgg atc cag cgc tgt aca gca gag tca ggt      624
Leu Lys Trp Leu Arg Asn Arg Ile Gln Arg Cys Thr Ala Glu Ser Gly
        195                 200                 205

tct ggc ctg ccg gaa gag tca gaa cct gag tcc tgg act ggc caa agg      672
Ser Gly Leu Pro Glu Glu Ser Glu Pro Glu Ser Trp Thr Gly Gln Arg
    210                 215                 220

gct gca gta gag ttc cag gac ctc atg cag ctc caa gac ctg gat ctc      720
Ala Ala Val Glu Phe Gln Asp Leu Met Gln Leu Gln Asp Leu Asp Leu
225                 230                 235                 240

agc tac gag aac ctg gct ttc ctc aaa ctc aag gcc ctg agc agt gta      768
Ser Tyr Glu Asn Leu Ala Phe Leu Lys Leu Lys Ala Leu Ser Ser Val
                245                 250                 255

aac ttt ggg cac agg caa gcg gtt gtg ggt gga ctt tcc aat ccc ctc      816
Asn Phe Gly His Arg Gln Ala Val Val Gly Gly Leu Ser Asn Pro Leu
            260                 265                 270

tcc ttc cct ggg tac ctc acc ctc cct ggc ttc tgt gtt aca gat tct      864
Ser Phe Pro Gly Tyr Leu Thr Leu Pro Gly Phe Cys Val Thr Asp Ser
        275                 280                 285

cag ctg gct gag tgc cgg ggc cct cct gaa gtc gag ggc gcc ccg ctc      912
Gln Leu Ala Glu Cys Arg Gly Pro Pro Glu Val Glu Gly Ala Pro Leu
    290                 295                 300

ttc tca ctc act gag gag agc ttc aag gcc tgc cac ctg acc ctg acc      960
Phe Ser Leu Thr Glu Glu Ser Phe Lys Ala Cys His Leu Thr Leu Thr
305                 310                 315                 320

ctg gat gat tac cta ttc att gcg ttc gtg ggc ttc gtg gtc tcc att     1008
Leu Asp Asp Tyr Leu Phe Ile Ala Phe Val Gly Phe Val Val Ser Ile
                325                 330                 335

gct tct gtg gcc acc aac ttc ctc ctg ggc atc act gcc aac tgc tgc     1056
Ala Ser Val Ala Thr Asn Phe Leu Leu Gly Ile Thr Ala Asn Cys Cys
            340                 345                 350
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cac cgc tgg agc aag gcc agt gaa gag gaa gag atc tga                1095
His Arg Trp Ser Lys Ala Ser Glu Glu Glu Glu Ile
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<210> 196
<211> 364
<212> PRT
<213> Homo sapiens

<400> 196

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Met Ala Ser Glu Thr Phe Asn Thr Glu Asp Pro Ala Gly Leu Met His
1               5                  10                  15

Ser Asp Ala Gly Thr Ser Cys Pro Val Leu Cys Thr Cys Arg Asn Gln
            20                  25                  30

Val Val Asp Cys Ser Ser Gln Arg Leu Phe Ser Val Pro Pro Asp Leu
        35                  40                  45

Pro Met Asp Thr Arg Asn Leu Ser Leu Ala His Asn Arg Ile Thr Ala
    50                  55                  60

Val Pro Pro Gly Tyr Leu Thr Cys Tyr Met Glu Leu Gln Val Leu Asp
65                  70                  75                  80

Leu His Asn Asn Ser Leu Met Glu Leu Pro Arg Gly Leu Phe Leu His
                85                  90                  95

Ala Lys Arg Leu Ala His Leu Asp Leu Ser Tyr Asn Asn Phe Ser His
            100                 105                 110

Val Pro Ala Asp Met Phe Gln Glu Ala His Gly Leu Val His Ile Asp
        115                 120                 125

Leu Ser His Asn Pro Trp Leu Arg Arg Val His Pro Gln Ala Phe Gln
    130                 135                 140

Gly Leu Met Gln Leu Arg Asp Leu Asp Leu Ser Tyr Gly Gly Leu Ala
145                 150                 155                 160

Phe Leu Ser Leu Glu Ala Leu Glu Gly Leu Pro Gly Leu Val Thr Leu
                165                 170                 175

Gln Ile Gly Gly Asn Pro Trp Val Cys Gly Cys Thr Met Glu Pro Leu
            180                 185                 190

Leu Lys Trp Leu Arg Asn Arg Ile Gln Arg Cys Thr Ala Glu Ser Gly
        195                 200                 205

Ser Gly Leu Pro Glu Glu Ser Glu Pro Glu Ser Trp Thr Gly Gln Arg
    210                 215                 220

Ala Ala Val Glu Phe Gln Asp Leu Met Gln Leu Gln Asp Leu Asp Leu
225                 230                 235                 240

Ser Tyr Glu Asn Leu Ala Phe Leu Lys Leu Lys Ala Leu Ser Ser Val
                245                 250                 255

Asn Phe Gly His Arg Gln Ala Val Val Gly Gly Leu Ser Asn Pro Leu
            260                 265                 270
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Ser Phe Pro Gly Tyr Leu Thr Leu Pro Gly Phe Cys Val Thr Asp Ser
275 280 285

Gln Leu Ala Glu Cys Arg Gly Pro Pro Glu Val Glu Gly Ala Pro Leu
290 295 300

Phe Ser Leu Thr Glu Glu Ser Phe Lys Ala Cys His Leu Thr Leu Thr
305 310 315 320

Leu Asp Asp Tyr Leu Phe Ile Ala Phe Val Gly Phe Val Val Ser Ile
325 330 335

Ala Ser Val Ala Thr Asn Phe Leu Leu Gly Ile Thr Ala Asn Cys Cys
340 345 350

His Arg Trp Ser Lys Ala Ser Glu Glu Glu Glu Ile
355 360

<210> 197
<211> 27
<212> DNA
<213> Homo sapiens

<400> 197
gggatttggt gtccaacacg aatttca 27

<210> 198
<211> 34
<212> DNA
<213> Homo sapiens

<400> 198
gagcctataa tatatgagcc agctacgagt tgga 34

<210> 199
<211> 32
<212> DNA
<213> Homo sapiens

<400> 199
gtcactgaat tctatcttct gggatttggt gc 32

<210> 200
<211> 32
<212> DNA
<213> Homo sapiens

<400> 200
aaacctgttt gtacagaggc atttattgag cc 32

<210> 201
<211> 35
<212> DNA
<213> Homo sapiens

<400> 201
gatatcattt tggggctgca tgatacaatt attgg 35

<210> 202
<211> 33
<212> DNA
<213> Homo sapiens

<400> 202
ctccaaccca gtgaacatca agttaaatcc cac 33

OCID: <WO_____03089583A2_I_>

<210> 203
<211> 36
<212> DNA
<213> Homo sapiens

<400> 203
ttaagctatt agttagttca tatgtcatgg gtttcc 36

<210> 204
<211> 36
<212> DNA
<213> Homo sapiens

<400> 204
ctcattaata cgatggcata gatacatgta agagag 36

<210> 205
<211> 50
<212> DNA
<213> Homo sapiens

<400> 205
atgttccatc taaatgaagc ctgagaaacc cagcactacc cacttgttag 50

<210> 206
<211> 50
<212> DNA
<213> Homo sapiens

<400> 206
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<210> 207
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<212> DNA
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aaatgtataa attctgcatg aaattggggg tggggcttgt actacttttg 50

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<211> 50
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<400> 208
atgttccatc taaatgaagc ctgagaaacc cagcactacc cacttgttag 50

<210> 209
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<212> DNA
<213> Homo sapiens

<400> 209
acatccatta tataacaggg ttaatatact tgtaaagaat agcacctaga 50

<210> 210
<211> 50
<212> DNA
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<400> 210
aaatatatat tttaaattgg ccaggcgcgg tggctcacgc ctataatccc 50

<210> 211
<211> 50
<212> DNA
<213> Homo sapiens

<400> 211

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<211> 50
<212> DNA
<213> Homo sapiens

<400> 212
tcccaaatat atatatatac acacacacac acacacacac acatatatat 50

<210> 213
<211> 50
<212> DNA
<213> Homo sapiens

<400> 213
cacacacaca tatatataca cacacatata tttataatca tttaacaaca 50

<210> 214
<211> 933
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)..(930)
<223>

<400> 214

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Met Ala Glu Met Asn Leu Thr Leu Val Thr Glu Phe Leu Leu Ile Ala
1               5                  10                  15

ttc act gaa tat cct gaa tgg gca ctc cct ctc ttc ctc ttg ttt tta      96
Phe Thr Glu Tyr Pro Glu Trp Ala Leu Pro Leu Phe Leu Leu Phe Leu
            20                  25                  30

ttt atg tat ctc atc acc gta ttg ggg aac tta gag atg att att ctg     144
Phe Met Tyr Leu Ile Thr Val Leu Gly Asn Leu Glu Met Ile Ile Leu
        35                  40                  45

atc ctc atg gat cac cag ctc cac gct cca atg tat ttc ctt ctg agt     192
Ile Leu Met Asp His Gln Leu His Ala Pro Met Tyr Phe Leu Leu Ser
    50                  55                  60

cac ctc gct ttc atg gac gtc tgc tac tca tct atc act gtc ccc cag     240
His Leu Ala Phe Met Asp Val Cys Tyr Ser Ser Ile Thr Val Pro Gln
65                  70                  75                  80

atg ctg gca gtg ctg ctg gag cat ggg gca gct tta tct tac aca cgc     288
Met Leu Ala Val Leu Leu Glu His Gly Ala Ala Leu Ser Tyr Thr Arg
                85                  90                  95

tgt gct gct cag ttc ttt ctg ttc acc ttc ttt ggt tcc atc gac tgc     336
Cys Ala Ala Gln Phe Phe Leu Phe Thr Phe Phe Gly Ser Ile Asp Cys
            100                 105                 110

tac ctc ttg gcc ctc atg gcc tat gac cgc tac ttg gct gtg tgc cag     384
Tyr Leu Leu Ala Leu Met Ala Tyr Asp Arg Tyr Leu Ala Val Cys Gln
        115                 120                 125

ccc ctg ctt tat gtc acc atc ctg aca cag cag gcc cgc ttg agt ctt     432
Pro Leu Leu Tyr Val Thr Ile Leu Thr Gln Gln Ala Arg Leu Ser Leu
    130                 135                 140

gtg gct ggg gct tac gtt gct ggt ctc atc agt gcc ttg gtg cgg aca     480
Val Ala Gly Ala Tyr Val Ala Gly Leu Ile Ser Ala Leu Val Arg Thr
145                 150                 155                 160

gtc tca gcc ttc act ctc tcc ttc tgt gga acc agt gag att gac ttt     528
Val Ser Ala Phe Thr Leu Ser Phe Cys Gly Thr Ser Glu Ile Asp Phe
                165                 170                 175

att ttc tgt gac ctc cct cct ctg tta aag ttg acc tgt ggg gag agc     576
Ile Phe Cys Asp Leu Pro Pro Leu Leu Lys Leu Thr Cys Gly Glu Ser
            180                 185                 190
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tac act caa gaa gtg ctg att att atg ttt gcc att ttt gtc atc cct      624
Tyr Thr Gln Glu Val Leu Ile Ile Met Phe Ala Ile Phe Val Ile Pro
        195                 200                 205

gct tcc atg gtg gtg atc ttg gtg tcc tac ctg ttt atc atc gtg gcc      672
Ala Ser Met Val Val Ile Leu Val Ser Tyr Leu Phe Ile Ile Val Ala
    210                 215                 220

atc atg ggg atc cct gct gga agc cag gcc aag acc ttc tcc acc tgc      720
Ile Met Gly Ile Pro Ala Gly Ser Gln Ala Lys Thr Phe Ser Thr Cys
225                 230                 235                 240

acc tcc cac ctc act gct gtg tca ctc ttc ttt ggt acc ctc atc ttc      768
Thr Ser His Leu Thr Ala Val Ser Leu Phe Phe Gly Thr Leu Ile Phe
                245                 250                 255

atg tac ttg aga ggt aac tca gat cag tct tcg gag aag aat cgg gta      816
Met Tyr Leu Arg Gly Asn Ser Asp Gln Ser Ser Glu Lys Asn Arg Val
            260                 265                 270

gtg tct gtg ctt tac aca gag gtc atc ccc atg ttg aat ccc ctc atc      864
Val Ser Val Leu Tyr Thr Glu Val Ile Pro Met Leu Asn Pro Leu Ile
        275                 280                 285

tac agc ctg agg aac aag gaa gtg aag gag gcc ctg aga aaa att ctc      912
Tyr Ser Leu Arg Asn Lys Glu Val Lys Glu Ala Leu Arg Lys Ile Leu
    290                 295                 300

aat aga gcc aag ttg tcc taa                                        933
Asn Arg Ala Lys Leu Ser
305                 310
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<210> 215
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<212> PRT
<213> Homo sapiens

<400> 215

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Met Ala Glu Met Asn Leu Thr Leu Val Thr Glu Phe Leu Leu Ile Ala
1               5                   10                  15

Phe Thr Glu Tyr Pro Glu Trp Ala Leu Pro Leu Phe Leu Leu Phe Leu
            20                  25                  30

Phe Met Tyr Leu Ile Thr Val Leu Gly Asn Leu Glu Met Ile Ile Leu
        35                  40                  45

Ile Leu Met Asp His Gln Leu His Ala Pro Met Tyr Phe Leu Leu Ser
    50                  55                  60

His Leu Ala Phe Met Asp Val Cys Tyr Ser Ser Ile Thr Val Pro Gln
65                  70                  75                  80

Met Leu Ala Val Leu Leu Glu His Gly Ala Ala Leu Ser Tyr Thr Arg
                85                  90                  95

Cys Ala Ala Gln Phe Phe Leu Phe Thr Phe Phe Gly Ser Ile Asp Cys
            100                 105                 110

Tyr Leu Leu Ala Leu Met Ala Tyr Asp Arg Tyr Leu Ala Val Cys Gln
        115                 120                 125

Pro Leu Leu Tyr Val Thr Ile Leu Thr Gln Gln Ala Arg Leu Ser Leu
    130                 135                 140

Val Ala Gly Ala Tyr Val Ala Gly Leu Ile Ser Ala Leu Val Arg Thr
145                 150                 155                 160
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Val Ser Ala Phe Thr Leu Ser Phe Cys Gly Thr Ser Glu Ile Asp Phe
                165                 170                 175

Ile Phe Cys Asp Leu Pro Pro Leu Leu Lys Leu Thr Cys Gly Glu Ser
            180                 185                 190

Tyr Thr Gln Glu Val Leu Ile Ile Met Phe Ala Ile Phe Val Ile Pro
        195                 200                 205

Ala Ser Met Val Val Ile Leu Val Ser Tyr Leu Phe Ile Ile Val Ala
    210                 215                 220

Ile Met Gly Ile Pro Ala Gly Ser Gln Ala Lys Thr Phe Ser Thr Cys
225                 230                 235                 240

Thr Ser His Leu Thr Ala Val Ser Leu Phe Phe Gly Thr Leu Ile Phe
                245                 250                 255

Met Tyr Leu Arg Gly Asn Ser Asp Gln Ser Ser Glu Lys Asn Arg Val
            260                 265                 270

Val Ser Val Leu Tyr Thr Glu Val Ile Pro Met Leu Asn Pro Leu Ile
        275                 280                 285

Tyr Ser Leu Arg Asn Lys Glu Val Lys Glu Ala Leu Arg Lys Ile Leu
    290                 295                 300

Asn Arg Ala Lys Leu Ser
305                 310
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<210> 216
<211> 933
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<220>
<221> CDS
<222> (1)..(930)
<223>

<400> 216

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atg gaa ggc aac aag aca tgg atc aca gac atc acc ttg ccg cga ttc      48
Met Glu Gly Asn Lys Thr Trp Ile Thr Asp Ile Thr Leu Pro Arg Phe
1               5                   10                  15

cag gtt ggt cca gca ctg gag att ctc ctc tgt gga ctt ttc tct gcc      96
Gln Val Gly Pro Ala Leu Glu Ile Leu Leu Cys Gly Leu Phe Ser Ala
            20                  25                  30

ttc tat aca ctc acc ctg ctg ggg aat ggg gtc atc ttt ggg att atc     144
Phe Tyr Thr Leu Thr Leu Leu Gly Asn Gly Val Ile Phe Gly Ile Ile
        35                  40                  45

tgc ctg gac tgt aag ctt cac aca ccc atg tac ttc ttc ctc tca cac     192
Cys Leu Asp Cys Lys Leu His Thr Pro Met Tyr Phe Phe Leu Ser His
    50                  55                  60

ctg gcc att gtt gac ata tcc tat gct tcc aac tat gtc ccc aag atg     240
Leu Ala Ile Val Asp Ile Ser Tyr Ala Ser Asn Tyr Val Pro Lys Met
65                  70                  75                  80

ctg acg aat ctt atg aac cag gaa agc acc atc tcc ttt ttt cca tgc     288
Leu Thr Asn Leu Met Asn Gln Glu Ser Thr Ile Ser Phe Phe Pro Cys
                85                  90                  95

ata atg cag aca ttc ttg tat ttg gct ttt gct cac gta gag tgt ctg     336
Ile Met Gln Thr Phe Leu Tyr Leu Ala Phe Ala His Val Glu Cys Leu
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XCID: <WO 03089583A2 I. >

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            100                 105                 110

att ttg gtg gtg atg tcc tat gat cgc tat gcg gac atc tgc cac ccc      384
Ile Leu Val Val Met Ser Tyr Asp Arg Tyr Ala Asp Ile Cys His Pro
        115                 120                 125

tta cgt tac aat agc ctc atg agc tgg aga gtg tgc act gtc ctg gct      432
Leu Arg Tyr Asn Ser Leu Met Ser Trp Arg Val Cys Thr Val Leu Ala
    130                 135                 140

gtg gct tcc tgg gtg ttc agc ttc ctc ctg gct ctg gtc cct tta gtt      480
Val Ala Ser Trp Val Phe Ser Phe Leu Leu Ala Leu Val Pro Leu Val
145                 150                 155                 160

ctc atc ctg agc ctg ccc ttc tgc ggg cct cat gaa atc aac cac ttc      528
Leu Ile Leu Ser Leu Pro Phe Cys Gly Pro His Glu Ile Asn His Phe
                165                 170                 175

ttc tgt gaa atc ctg tct gtc ctc aag ttg gcc tgt gct gac acc tgg      576
Phe Cys Glu Ile Leu Ser Val Leu Lys Leu Ala Cys Ala Asp Thr Trp
            180                 185                 190

ctc aac cag gtg gtc atc ttt gca gcc tgc gtg ttc atc ctg gtg ggg      624
Leu Asn Gln Val Val Ile Phe Ala Ala Cys Val Phe Ile Leu Val Gly
        195                 200                 205

cca ctc tgc ctg gtg ctg gtc tcc tac ttg cgc atc ctg gcc gcc atc      672
Pro Leu Cys Leu Val Leu Val Ser Tyr Leu Arg Ile Leu Ala Ala Ile
    210                 215                 220

ttg agg atc cag tct ggg gag ggc cgc aga aag gcc ttc tcc acc tgc      720
Leu Arg Ile Gln Ser Gly Glu Gly Arg Arg Lys Ala Phe Ser Thr Cys
225                 230                 235                 240

tcc tcc cac ctt tgc gtg gtg gga ctc ttc ttt ggc agc gcc att gtc      768
Ser Ser His Leu Cys Val Val Gly Leu Phe Phe Gly Ser Ala Ile Val
                245                 250                 255

acg tac atg gcc ccc aag tcc cgc cat cct gag gag cag cag aaa gtt      816
Thr Tyr Met Ala Pro Lys Ser Arg His Pro Glu Glu Gln Gln Lys Val
            260                 265                 270

ctt tcc ctg ttt tac agc ctt ttc aat cca atg ctg aac ccc ctg ata      864
Leu Ser Leu Phe Tyr Ser Leu Phe Asn Pro Met Leu Asn Pro Leu Ile
        275                 280                 285

tat agc cta agg aat gca gag gtc aag ggc gcc ctg agg agg gca ctg      912
Tyr Ser Leu Arg Asn Ala Glu Val Lys Gly Ala Leu Arg Arg Ala Leu
    290                 295                 300

agg aag gag agg ctg acg tga                                          933
Arg Lys Glu Arg Leu Thr
305                 310


<210>  217
<211>  310
<212>  PRT
<213>  Homo sapiens

<400>  217

Met Glu Gly Asn Lys Thr Trp Ile Thr Asp Ile Thr Leu Pro Arg Phe
1               5                   10                  15


Gln Val Gly Pro Ala Leu Glu Ile Leu Leu Cys Gly Leu Phe Ser Ala
            20                  25                  30


Phe Tyr Thr Leu Thr Leu Leu Gly Asn Gly Val Ile Phe Gly Ile Ile
        35                  40                  45


Cys Leu Asp Cys Lys Leu His Thr Pro Met Tyr Phe Phe Leu Ser His
    50                  55                  60


Leu Ala Ile Val Asp Ile Ser Tyr Ala Ser Asn Tyr Val Pro Lys Met
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DOCID: <WO_____03089583A2_I_>

65 70 75 80

Leu Thr Asn Leu Met Asn Gln Glu Ser Thr Ile Ser Phe Phe Pro Cys
85 90 95

Ile Met Gln Thr Phe Leu Tyr Leu Ala Phe Ala His Val Glu Cys Leu
100 105 110

Ile Leu Val Val Met Ser Tyr Asp Arg Tyr Ala Asp Ile Cys His Pro
115 120 125

Leu Arg Tyr Asn Ser Leu Met Ser Trp Arg Val Cys Thr Val Leu Ala
130 135 140

Val Ala Ser Trp Val Phe Ser Phe Leu Leu Ala Leu Val Pro Leu Val
145 150 155 160

Leu Ile Leu Ser Leu Pro Phe Cys Gly Pro His Glu Ile Asn His Phe
165 170 175

Phe Cys Glu Ile Leu Ser Val Leu Lys Leu Ala Cys Ala Asp Thr Trp
180 185 190

Leu Asn Gln Val Val Ile Phe Ala Ala Cys Val Phe Ile Leu Val Gly
195 200 205

Pro Leu Cys Leu Val Leu Val Ser Tyr Leu Arg Ile Leu Ala Ala Ile
210 215 220

Leu Arg Ile Gln Ser Gly Glu Gly Arg Arg Lys Ala Phe Ser Thr Cys
225 230 235 240

Ser Ser His Leu Cys Val Val Gly Leu Phe Phe Gly Ser Ala Ile Val
245 250 255

Thr Tyr Met Ala Pro Lys Ser Arg His Pro Glu Glu Gln Gln Lys Val
260 265 270

Leu Ser Leu Phe Tyr Ser Leu Phe Asn Pro Met Leu Asn Pro Leu Ile
275 280 285

Tyr Ser Leu Arg Asn Ala Glu Val Lys Gly Ala Leu Arg Arg Ala Leu
290 295 300

Arg Lys Glu Arg Leu Thr
305 310

<210> 218
<211> 927
<212> DNA
<213> Homo sapiens

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<221> CDS
<222> (1)..(924)
<223>

<400> 218
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Met Ala Met Asp Asn Val Thr Ala Val Phe Gln Phe Leu Leu Ile Gly
1 5 10 15

att tct aac tat cct caa tgg aga gac acg ttt ttc aca tta gtg ctg 96

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Ile Ser Asn Tyr Pro Gln Trp Arg Asp Thr Phe Phe Thr Leu Val Leu
            20                  25                  30

ata att tac ctc agc aca ttg ttg ggg aat gga ttt atg atc ttt ctt      144
Ile Ile Tyr Leu Ser Thr Leu Leu Gly Asn Gly Phe Met Ile Phe Leu
        35                  40                  45

att cac ttt gac ccc aac ctc cac act cca atc tac ttc ttc ctt agt      192
Ile His Phe Asp Pro Asn Leu His Thr Pro Ile Tyr Phe Phe Leu Ser
    50                  55                  60

aac ctg tct ttc tta gac ctt tgt tat gga aca gct tcc atg ccc cag      240
Asn Leu Ser Phe Leu Asp Leu Cys Tyr Gly Thr Ala Ser Met Pro Gln
65                  70                  75                  80

gct ttg gtg cat tgt ttc tct acc cat ccc tac ctc tct tat ccc cga      288
Ala Leu Val His Cys Phe Ser Thr His Pro Tyr Leu Ser Tyr Pro Arg
                85                  90                  95

tgt ttg gct caa acg agt gtc tcc ttg gct ttg gcc aca gca gag tgc      336
Cys Leu Ala Gln Thr Ser Val Ser Leu Ala Leu Ala Thr Ala Glu Cys
            100                 105                 110

ctc cta ctg gct gcc atg gcc tat gac cgt gtg gtt gct atc agc aat      384
Leu Leu Leu Ala Ala Met Ala Tyr Asp Arg Val Val Ala Ile Ser Asn
        115                 120                 125

ccc ctg cgt tat tca gtg gtt atg aat ggc cca gta tgt gtc tgc ttg      432
Pro Leu Arg Tyr Ser Val Val Met Asn Gly Pro Val Cys Val Cys Leu
    130                 135                 140

gtt gct acc tca tgg ggg aca tca ctt gtg ctc act gcc atg ctc atc      480
Val Ala Thr Ser Trp Gly Thr Ser Leu Val Leu Thr Ala Met Leu Ile
145                 150                 155                 160

cta tcc ctg agg ctt cac ttc tgt ggg gct aat gtc atc aac cat ttt      528
Leu Ser Leu Arg Leu His Phe Cys Gly Ala Asn Val Ile Asn His Phe
                165                 170                 175

gcc tgt gag att ctc tcc ctc att aag ctg acc tgt tct gat acc agc      576
Ala Cys Glu Ile Leu Ser Leu Ile Lys Leu Thr Cys Ser Asp Thr Ser
            180                 185                 190

ctc aat gaa ttt atg atc ctc atc acc agt atc ttc acc ctg ctg cta      624
Leu Asn Glu Phe Met Ile Leu Ile Thr Ser Ile Phe Thr Leu Leu Leu
        195                 200                 205

cca ttt ggg ttt gtt ctc ctc tcc tac ata cga att gct atg gct atc      672
Pro Phe Gly Phe Val Leu Leu Ser Tyr Ile Arg Ile Ala Met Ala Ile
    210                 215                 220

ata agg att cgc tca ctc cag ggc agg ctc aag gcc ttt acc aca tgt      720
Ile Arg Ile Arg Ser Leu Gln Gly Arg Leu Lys Ala Phe Thr Thr Cys
225                 230                 235                 240

ggc tct cac ctg acc gtg gtg aca atc ttc tat ggg tca gcc atc tcc      768
Gly Ser His Leu Thr Val Val Thr Ile Phe Tyr Gly Ser Ala Ile Ser
                245                 250                 255

atg tat atg aaa act cag tcc aag tcc tac cct gac cag gac aag ttt      816
Met Tyr Met Lys Thr Gln Ser Lys Ser Tyr Pro Asp Gln Asp Lys Phe
            260                 265                 270

atc tca gtg ttt tat gga gct ttg aca ccc atg ttg aac ccc ctg ata      864
Ile Ser Val Phe Tyr Gly Ala Leu Thr Pro Met Leu Asn Pro Leu Ile
        275                 280                 285

tat agc ctg aga aaa aaa gat gtt aaa cgg gca ata agg aaa gtt atg      912
Tyr Ser Leu Arg Lys Lys Asp Val Lys Arg Ala Ile Arg Lys Val Met
    290                 295                 300

ttg aaa agg aca tga                                                 927
Leu Lys Arg Thr
305
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<210> 219
<211> 308
<212> PRT

160 200 PCT FINAL.ST25

<213> Homo sapiens

<400> 219

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1               5                  10                  15

Ile Ser Asn Tyr Pro Gln Trp Arg Asp Thr Phe Phe Thr Leu Val Leu
            20                  25                  30

Ile Ile Tyr Leu Ser Thr Leu Leu Gly Asn Gly Phe Met Ile Phe Leu
        35                  40                  45

Ile His Phe Asp Pro Asn Leu His Thr Pro Ile Tyr Phe Phe Leu Ser
    50                  55                  60

Asn Leu Ser Phe Leu Asp Leu Cys Tyr Gly Thr Ala Ser Met Pro Gln
65                  70                  75                  80

Ala Leu Val His Cys Phe Ser Thr His Pro Tyr Leu Ser Tyr Pro Arg
                85                  90                  95

Cys Leu Ala Gln Thr Ser Val Ser Leu Ala Leu Ala Thr Ala Glu Cys
            100                 105                 110

Leu Leu Leu Ala Ala Met Ala Tyr Asp Arg Val Val Ala Ile Ser Asn
        115                 120                 125

Pro Leu Arg Tyr Ser Val Val Met Asn Gly Pro Val Cys Val Cys Leu
    130                 135                 140

Val Ala Thr Ser Trp Gly Thr Ser Leu Val Leu Thr Ala Met Leu Ile
145                 150                 155                 160

Leu Ser Leu Arg Leu His Phe Cys Gly Ala Asn Val Ile Asn His Phe
                165                 170                 175

Ala Cys Glu Ile Leu Ser Leu Ile Lys Leu Thr Cys Ser Asp Thr Ser
            180                 185                 190

Leu Asn Glu Phe Met Ile Leu Ile Thr Ser Ile Phe Thr Leu Leu Leu
        195                 200                 205

Pro Phe Gly Phe Val Leu Leu Ser Tyr Ile Arg Ile Ala Met Ala Ile
    210                 215                 220

Ile Arg Ile Arg Ser Leu Gln Gly Arg Leu Lys Ala Phe Thr Thr Cys
225                 230                 235                 240

Gly Ser His Leu Thr Val Val Thr Ile Phe Tyr Gly Ser Ala Ile Ser
                245                 250                 255

Met Tyr Met Lys Thr Gln Ser Lys Ser Tyr Pro Asp Gln Asp Lys Phe
            260                 265                 270

Ile Ser Val Phe Tyr Gly Ala Leu Thr Pro Met Leu Asn Pro Leu Ile
        275                 280                 285

Tyr Ser Leu Arg Lys Lys Asp Val Lys Arg Ala Ile Arg Lys Val Met
    290                 295                 300
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XCID: <WO ____03089583A2_I_>

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Leu Lys Arg Thr
305


<210>  220
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<212>  DNA
<213>  Homo sapiens

<220>
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<222>  (1)..(1005)
<223>

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Met Glu Ser Ser Phe Ser Phe Gly Val Ile Leu Ala Val Leu Ala Ser
1               5                  10                  15

ctc atc att gct act aac aca cta gtg gct gtg gct gtg ctg ctg ttg       96
Leu Ile Ile Ala Thr Asn Thr Leu Val Ala Val Ala Val Leu Leu Leu
            20                  25                  30

atc cac aag aat gat ggt gtc agt ctc tgc ttc acc ttg aat ctg gct      144
Ile His Lys Asn Asp Gly Val Ser Leu Cys Phe Thr Leu Asn Leu Ala
        35                  40                  45

gtg gct gac acc ttg att ggt gtg gcc atc tct ggc cta ctc aca gac      192
Val Ala Asp Thr Leu Ile Gly Val Ala Ile Ser Gly Leu Leu Thr Asp
    50                  55                  60

cag ctc tcc agc cct tct cgg ccc aca cag aag acc ctg tgc agc ctg      240
Gln Leu Ser Ser Pro Ser Arg Pro Thr Gln Lys Thr Leu Cys Ser Leu
65                  70                  75                  80

cgg atg gca ttt gtc act tcc tcc gca gct gcc tct gtc ctc acg gtc      288
Arg Met Ala Phe Val Thr Ser Ser Ala Ala Ala Ser Val Leu Thr Val
                85                  90                  95

atg ctg atc acc ttt gac agg tac ctt gcc atc aag cag ccc ttc cgc      336
Met Leu Ile Thr Phe Asp Arg Tyr Leu Ala Ile Lys Gln Pro Phe Arg
            100                 105                 110

tac ttg aag atc atg agt ggg ttc gtg gcc ggg gcc tgc att gcc ggg      384
Tyr Leu Lys Ile Met Ser Gly Phe Val Ala Gly Ala Cys Ile Ala Gly
        115                 120                 125

ctg tgg tta gtg tct tac ctc att ggc ttc ctc cca ctc gga atc ccc      432
Leu Trp Leu Val Ser Tyr Leu Ile Gly Phe Leu Pro Leu Gly Ile Pro
    130                 135                 140

atg ttc cag cag act gcc tac aaa ggg cag tgc agc ttc ttt gct gta      480
Met Phe Gln Gln Thr Ala Tyr Lys Gly Gln Cys Ser Phe Phe Ala Val
145                 150                 155                 160

ttt cac cct cac ttc gtg ctg acc ctc tcc tgc gtt ggc ttc ttc cca      528
Phe His Pro His Phe Val Leu Thr Leu Ser Cys Val Gly Phe Phe Pro
                165                 170                 175

gcc atg ctc ctc ttt gtc ttc ttc tac tgc gac atg ctc aag att gcc      576
Ala Met Leu Leu Phe Val Phe Phe Tyr Cys Asp Met Leu Lys Ile Ala
            180                 185                 190

tcc atg cac agc cag cag att cga aag atg gaa cat gca gga gcc atg      624
Ser Met His Ser Gln Gln Ile Arg Lys Met Glu His Ala Gly Ala Met
        195                 200                 205

gct gga ggt tat cga tcc cca cgg act ccc agc gac ttc aaa gct ctc      672
Ala Gly Gly Tyr Arg Ser Pro Arg Thr Pro Ser Asp Phe Lys Ala Leu
    210                 215                 220

cgt act gtg tct gtt ctc att ggg agc ttt gct cta tcc tgg acc ccc      720
Arg Thr Val Ser Val Leu Ile Gly Ser Phe Ala Leu Ser Trp Thr Pro
225                 230                 235                 240

ttc ctt atc act ggc att gtg cag gtg gcc tgc cag gag tgt cac ctc      768
Phe Leu Ile Thr Gly Ile Val Gln Val Ala Cys Gln Glu Cys His Leu
                245                 250                 255
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SDOCID: <WO 03089583A2_I_>

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tac cta gtg ctg gaa cgg tac ctg tgg ctg ctc ggc gtg ggc aac tcc      816
Tyr Leu Val Leu Glu Arg Tyr Leu Trp Leu Leu Gly Val Gly Asn Ser
            260                 265                 270

ctg ctc aac cca ctc atc tat gcc tat tgg cag aag gag gtg cga ctg      864
Leu Leu Asn Pro Leu Ile Tyr Ala Tyr Trp Gln Lys Glu Val Arg Leu
        275                 280                 285

cag ctc tac cac atg gcc cta gga gtg aag aag gtg ctc acc tca ttc      912
Gln Leu Tyr His Met Ala Leu Gly Val Lys Lys Val Leu Thr Ser Phe
    290                 295                 300

ctc ctc ttt ctc tcg gcc agg aat tgt ggc cca gag agg ccc agg gaa      960
Leu Leu Phe Leu Ser Ala Arg Asn Cys Gly Pro Glu Arg Pro Arg Glu
305                 310                 315                 320

agt tcc tgt cac atc gtc act atc tcc agc tca gag ttt gat ggc taa     1008
Ser Ser Cys His Ile Val Thr Ile Ser Ser Ser Glu Phe Asp Gly
                325                 330                 335
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<210> 221
<211> 335
<212> PRT
<213> Homo sapiens

<400> 221

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Met Glu Ser Ser Phe Ser Phe Gly Val Ile Leu Ala Val Leu Ala Ser
1               5                   10                  15

Leu Ile Ile Ala Thr Asn Thr Leu Val Ala Val Ala Val Leu Leu Leu
            20                  25                  30

Ile His Lys Asn Asp Gly Val Ser Leu Cys Phe Thr Leu Asn Leu Ala
        35                  40                  45

Val Ala Asp Thr Leu Ile Gly Val Ala Ile Ser Gly Leu Leu Thr Asp
    50                  55                  60

Gln Leu Ser Ser Pro Ser Arg Pro Thr Gln Lys Thr Leu Cys Ser Leu
65                  70                  75                  80

Arg Met Ala Phe Val Thr Ser Ser Ala Ala Ala Ser Val Leu Thr Val
                85                  90                  95

Met Leu Ile Thr Phe Asp Arg Tyr Leu Ala Ile Lys Gln Pro Phe Arg
            100                 105                 110

Tyr Leu Lys Ile Met Ser Gly Phe Val Ala Gly Ala Cys Ile Ala Gly
        115                 120                 125

Leu Trp Leu Val Ser Tyr Leu Ile Gly Phe Leu Pro Leu Gly Ile Pro
    130                 135                 140

Met Phe Gln Gln Thr Ala Tyr Lys Gly Gln Cys Ser Phe Phe Ala Val
145                 150                 155                 160

Phe His Pro His Phe Val Leu Thr Leu Ser Cys Val Gly Phe Phe Pro
                165                 170                 175

Ala Met Leu Leu Phe Val Phe Phe Tyr Cys Asp Met Leu Lys Ile Ala
            180                 185                 190

Ser Met His Ser Gln Gln Ile Arg Lys Met Glu His Ala Gly Ala Met
        195                 200                 205
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OCID: <WO 03089583A2 I >

Ala Gly Gly Tyr Arg Ser Pro Arg Thr Pro Ser Asp Phe Lys Ala Leu
210 215 220

Arg Thr Val Ser Val Leu Ile Gly Ser Phe Ala Leu Ser Trp Thr Pro
225 230 235 240

Phe Leu Ile Thr Gly Ile Val Gln Val Ala Cys Gln Glu Cys His Leu
245 250 255

Tyr Leu Val Leu Glu Arg Tyr Leu Trp Leu Leu Gly Val Gly Asn Ser
260 265 270

Leu Leu Asn Pro Leu Ile Tyr Ala Tyr Trp Gln Lys Glu Val Arg Leu
275 280 285

Gln Leu Tyr His Met Ala Leu Gly Val Lys Lys Val Leu Thr Ser Phe
290 295 300

Leu Leu Phe Leu Ser Ala Arg Asn Cys Gly Pro Glu Arg Pro Arg Glu
305 310 315 320

Ser Ser Cys His Ile Val Thr Ile Ser Ser Ser Glu Phe Asp Gly
325 330 335

<210> 222
<211> 975
<212> DNA
<213> Homo sapiens

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<221> CDS
<222> (1)..(972)
<223>

<400> 222
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Met Arg Pro Gln Asp Ser Thr Gly Val Ala Glu Leu Gln Glu Pro Gly
1 5 10 15

ctg ccg cta acg gac gat gca ccc ccg ggc gcc act gag gag ccg gcg 96
Leu Pro Leu Thr Asp Asp Ala Pro Pro Gly Ala Thr Glu Glu Pro Ala
20 25 30

gcc gcc gag gca gct ggg gcg cca gac cgc gtg ggc tct tta ttt gtt 144
Ala Ala Glu Ala Ala Gly Ala Pro Asp Arg Val Gly Ser Leu Phe Val
35 40 45

aaa aaa gtg caa gac gtc cat gct gta gag att agt gcg ttt cga tgt 192
Lys Lys Val Gln Asp Val His Ala Val Glu Ile Ser Ala Phe Arg Cys
50 55 60

gtg ttc caa atg cta gtt gtt atc cct tgc tta ata tac aga aaa act 240
Val Phe Gln Met Leu Val Val Ile Pro Cys Leu Ile Tyr Arg Lys Thr
65 70 75 80

ggg ttt ata ggc cca aaa ggt caa cga att ttc ctc att ctc aga gga 288
Gly Phe Ile Gly Pro Lys Gly Gln Arg Ile Phe Leu Ile Leu Arg Gly
85 90 95

gtc ctt ggt tct acc gcc atg atg ctt ata tac tat gct tac cag aca 336
Val Leu Gly Ser Thr Ala Met Met Leu Ile Tyr Tyr Ala Tyr Gln Thr
100 105 110

atg tcc ctc gct gat gcc aca gtt atc acg ttt agc agt cca gtg ttt 384
Met Ser Leu Ala Asp Ala Thr Val Ile Thr Phe Ser Ser Pro Val Phe
115 120 125

acg tcc ata ttt gct tgg ata tgt ctc aag gaa aaa tat agc cct tgg 432
Thr Ser Ile Phe Ala Trp Ile Cys Leu Lys Glu Lys Tyr Ser Pro Trp

DOCID: <WO_____03089583A2_I_>

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    130                 135                 140

gat gct ctt ttc acc gtg ttc aca atc act gga gtg atc ctt atc gtg      480
Asp Ala Leu Phe Thr Val Phe Thr Ile Thr Gly Val Ile Leu Ile Val
145                 150                 155                 160

aga cca cca ttt ttg ttt ggt tcc gac act tcg ggg atg gaa gaa agc      528
Arg Pro Pro Phe Leu Phe Gly Ser Asp Thr Ser Gly Met Glu Glu Ser
                165                 170                 175

tat tca ggc cac ctt aag gga aca ttc gca gca att gga agt gcc gta      576
Tyr Ser Gly His Leu Lys Gly Thr Phe Ala Ala Ile Gly Ser Ala Val
            180                 185                 190

ttt gct gca tcg act cta gtt atc cta aga aaa atg gga aaa tct gtg      624
Phe Ala Ala Ser Thr Leu Val Ile Leu Arg Lys Met Gly Lys Ser Val
        195                 200                 205

gac tac ttt ctg agc att tgg tat tat gta gta ctt ggc ctc gtt gaa      672
Asp Tyr Phe Leu Ser Ile Trp Tyr Tyr Val Val Leu Gly Leu Val Glu
    210                 215                 220

agt gtc atc atc ctc tct gta tta gga gag tgg agt ctg cct tac tgt      720
Ser Val Ile Ile Leu Ser Val Leu Gly Glu Trp Ser Leu Pro Tyr Cys
225                 230                 235                 240

ggg ttg gac agg cta ttt ctc ata ttc att ggg ctc ttt ggt ttg ggg      768
Gly Leu Asp Arg Leu Phe Leu Ile Phe Ile Gly Leu Phe Gly Leu Gly
                245                 250                 255

ggt cag ata ttt atc aca aaa gca ctt caa ata gaa aaa gca ggg cca      816
Gly Gln Ile Phe Ile Thr Lys Ala Leu Gln Ile Glu Lys Ala Gly Pro
            260                 265                 270

gta gca ata atg aag aca atg gat gtg gtc ttt gct ttt atc ttt cag      864
Val Ala Ile Met Lys Thr Met Asp Val Val Phe Ala Phe Ile Phe Gln
        275                 280                 285

att att ttc ttt aat aat gtg cca acg tgg tgg aca gtg ggt ggt gct      912
Ile Ile Phe Phe Asn Asn Val Pro Thr Trp Trp Thr Val Gly Gly Ala
    290                 295                 300

ctc tgc gta gta gcc agt aat gtt gga gcg gcc att cgt aaa tgg tac      960
Leu Cys Val Val Ala Ser Asn Val Gly Ala Ala Ile Arg Lys Trp Tyr
305                 310                 315                 320

caa agt tcc aaa tga                                                  975
Gln Ser Ser Lys
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<210> 223
<211> 324
<212> PRT
<213> Homo sapiens

<400> 223

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Met Arg Pro Gln Asp Ser Thr Gly Val Ala Glu Leu Gln Glu Pro Gly
1               5                   10                  15

Leu Pro Leu Thr Asp Asp Ala Pro Pro Gly Ala Thr Glu Glu Pro Ala
            20                  25                  30

Ala Ala Glu Ala Ala Gly Ala Pro Asp Arg Val Gly Ser Leu Phe Val
        35                  40                  45

Lys Lys Val Gln Asp Val His Ala Val Glu Ile Ser Ala Phe Arg Cys
    50                  55                  60

Val Phe Gln Met Leu Val Val Ile Pro Cys Leu Ile Tyr Arg Lys Thr
65                  70                  75                  80

Gly Phe Ile Gly Pro Lys Gly Gln Arg Ile Phe Leu Ile Leu Arg Gly
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85 90 95

Val Leu Gly Ser Thr Ala Met Met Leu Ile Tyr Tyr Ala Tyr Gln Thr
100 105 110

Met Ser Leu Ala Asp Ala Thr Val Ile Thr Phe Ser Ser Pro Val Phe
115 120 125

Thr Ser Ile Phe Ala Trp Ile Cys Leu Lys Glu Lys Tyr Ser Pro Trp
130 135 140

Asp Ala Leu Phe Thr Val Phe Thr Ile Thr Gly Val Ile Leu Ile Val
145 150 155 160

Arg Pro Pro Phe Leu Phe Gly Ser Asp Thr Ser Gly Met Glu Glu Ser
165 170 175

Tyr Ser Gly His Leu Lys Gly Thr Phe Ala Ala Ile Gly Ser Ala Val
180 185 190

Phe Ala Ala Ser Thr Leu Val Ile Leu Arg Lys Met Gly Lys Ser Val
195 200 205

Asp Tyr Phe Leu Ser Ile Trp Tyr Tyr Val Val Leu Gly Leu Val Glu
210 215 220

Ser Val Ile Ile Leu Ser Val Leu Gly Glu Trp Ser Leu Pro Tyr Cys
225 230 235 240

Gly Leu Asp Arg Leu Phe Leu Ile Phe Ile Gly Leu Phe Gly Leu Gly
245 250 255

Gly Gln Ile Phe Ile Thr Lys Ala Leu Gln Ile Glu Lys Ala Gly Pro
260 265 270

Val Ala Ile Met Lys Thr Met Asp Val Val Phe Ala Phe Ile Phe Gln
275 280 285

Ile Ile Phe Phe Asn Asn Val Pro Thr Trp Trp Thr Val Gly Gly Ala
290 295 300

Leu Cys Val Val Ala Ser Asn Val Gly Ala Ala Ile Arg Lys Trp Tyr
305 310 315 320

Gln Ser Ser Lys

<210> 224
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<212> DNA
<213> Homo sapiens

<220>
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<222> (1)..(873)
<223>

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Met Tyr Asn Met Ser Asp His Gly Thr Gly Leu Phe Ile Leu Leu Gly
1 5 10 15

atc cct gga ctt gag cag tac cac gtc tgg atc agc atc cca ttc tgc 96

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Ile Pro Gly Leu Glu Gln Tyr His Val Trp Ile Ser Ile Pro Phe Cys
            20                  25                  30

tta atc tat ctc atg gct gtc gtg gcc aat agt atc ctt ctc tac ctc      144
Leu Ile Tyr Leu Met Ala Val Val Ala Asn Ser Ile Leu Leu Tyr Leu
        35                  40                  45

att gtg gta gag cac agt ctt cat gca ccc atg ttc ttt ttc ctt tcc      192
Ile Val Val Glu His Ser Leu His Ala Pro Met Phe Phe Phe Leu Ser
    50                  55                  60

atg ctg gcc att act gat ctc ata ttg tcc acc aca tgt gtc ccc aaa      240
Met Leu Ala Ile Thr Asp Leu Ile Leu Ser Thr Thr Cys Val Pro Lys
65                  70                  75                  80

aca ctt agc atc ttc tgc ttt gtg ttg gac tca gct ata ctg ctg gcc      288
Thr Leu Ser Ile Phe Cys Phe Val Leu Asp Ser Ala Ile Leu Leu Ala
                85                  90                  95

atg gca ttt gac cgc tat atg gcc att tgc tca ccc ttg aga tac act      336
Met Ala Phe Asp Arg Tyr Met Ala Ile Cys Ser Pro Leu Arg Tyr Thr
            100                 105                 110

act att ctg act ccc aaa acc att gtc aaa att gct gtg gga ata tgt      384
Thr Ile Leu Thr Pro Lys Thr Ile Val Lys Ile Ala Val Gly Ile Cys
        115                 120                 125

ttc cga agt ttc tgt gtt ttt gtc cca tgt gtt ttc ctt gtg aat cgt      432
Phe Arg Ser Phe Cys Val Phe Val Pro Cys Val Phe Leu Val Asn Arg
    130                 135                 140

tta ccc ttc tgc agg aca cat atc att tct cac aca tac tgt gag cac      480
Leu Pro Phe Cys Arg Thr His Ile Ile Ser His Thr Tyr Cys Glu His
145                 150                 155                 160

ata ggt gtt gcc cag ctt gcc tgt gct gat atc tcc atc aat atc tgg      528
Ile Gly Val Ala Gln Leu Ala Cys Ala Asp Ile Ser Ile Asn Ile Trp
                165                 170                 175

tgt gga ttt tgt gtt ccc atc atg acg gtg atg aca gac gtg atc ctc      576
Cys Gly Phe Cys Val Pro Ile Met Thr Val Met Thr Asp Val Ile Leu
            180                 185                 190

att gct gtc tcc tac acc ctc atc ctc tgt gct gtc ttt tgc ctc ccc      624
Ile Ala Val Ser Tyr Thr Leu Ile Leu Cys Ala Val Phe Cys Leu Pro
        195                 200                 205

tcc caa gat gcc cgt cag aag gcc ctt tgc tcc tgt ggt tcc cat gtc      672
Ser Gln Asp Ala Arg Gln Lys Ala Leu Cys Ser Cys Gly Ser His Val
    210                 215                 220

tgt gtt atc ctc ata ttc tat ata cca gca ttc ttc tcc att ctt gcc      720
Cys Val Ile Leu Ile Phe Tyr Ile Pro Ala Phe Phe Ser Ile Leu Ala
225                 230                 235                 240

cat tgc ttt ggg cat aat gtc cct cat acc ttt cat att atg ttt gcc      768
His Cys Phe Gly His Asn Val Pro His Thr Phe His Ile Met Phe Ala
                245                 250                 255

aac ctt tat gta atc att cca cct gct ctc aac tct att gtc tac aga      816
Asn Leu Tyr Val Ile Ile Pro Pro Ala Leu Asn Ser Ile Val Tyr Arg
            260                 265                 270

ata aag acc aag caa atc cag aac aga atc ctt ttg ctc ttt ccc aag      864
Ile Lys Thr Lys Gln Ile Gln Asn Arg Ile Leu Leu Leu Phe Pro Lys
        275                 280                 285

ggg tcc cag tga                                                      876
Gly Ser Gln
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<210> 225
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<213> Homo sapiens

<400> 225

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Met Tyr Asn Met Ser Asp His Gly Thr Gly Leu Phe Ile Leu Leu Gly
1 5 10 15

Ile Pro Gly Leu Glu Gln Tyr His Val Trp Ile Ser Ile Pro Phe Cys
20 25 30

Leu Ile Tyr Leu Met Ala Val Val Ala Asn Ser Ile Leu Leu Tyr Leu
35 40 45

Ile Val Val Glu His Ser Leu His Ala Pro Met Phe Phe Phe Leu Ser
50 55 60

Met Leu Ala Ile Thr Asp Leu Ile Leu Ser Thr Thr Cys Val Pro Lys
65 70 75 80

Thr Leu Ser Ile Phe Cys Phe Val Leu Asp Ser Ala Ile Leu Leu Ala
85 90 95

Met Ala Phe Asp Arg Tyr Met Ala Ile Cys Ser Pro Leu Arg Tyr Thr
100 105 110

Thr Ile Leu Thr Pro Lys Thr Ile Val Lys Ile Ala Val Gly Ile Cys
115 120 125

Phe Arg Ser Phe Cys Val Phe Val Pro Cys Val Phe Leu Val Asn Arg
130 135 140

Leu Pro Phe Cys Arg Thr His Ile Ile Ser His Thr Tyr Cys Glu His
145 150 155 160

Ile Gly Val Ala Gln Leu Ala Cys Ala Asp Ile Ser Ile Asn Ile Trp
165 170 175

Cys Gly Phe Cys Val Pro Ile Met Thr Val Met Thr Asp Val Ile Leu
180 185 190

Ile Ala Val Ser Tyr Thr Leu Ile Leu Cys Ala Val Phe Cys Leu Pro
195 200 205

Ser Gln Asp Ala Arg Gln Lys Ala Leu Cys Ser Cys Gly Ser His Val
210 215 220

Cys Val Ile Leu Ile Phe Tyr Ile Pro Ala Phe Phe Ser Ile Leu Ala
225 230 235 240

His Cys Phe Gly His Asn Val Pro His Thr Phe His Ile Met Phe Ala
245 250 255

Asn Leu Tyr Val Ile Ile Pro Pro Ala Leu Asn Ser Ile Val Tyr Arg
260 265 270

Ile Lys Thr Lys Gln Ile Gln Asn Arg Ile Leu Leu Leu Phe Pro Lys
275 280 285

Gly Ser Gln
290

<210> 226
<211> 1949
<212> DNA

<213> Homo sapiens

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<222> (430)..(1164)
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<400> 226
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gtctctcgct gttcccagcc ttttccaggc gtgtgactta atccgtttcc acagccagac 180

cttttctccg tgagttcctc agccaggact gctgccatgc cggtgactgt tacccaccca 240

accgtcacga ccaccatgcg gtcccccacc gtcgtagggt cctctagggc cctgatccag 300

cccctgggcc tcctccgcct gctgcagctg gtgtccacct gcgtggcctt gtcactggtg 360

gccagcgtgg gcgcctggaa ggggcctatg ggtaactggt ccatgttcac ctagtgtttc 420

tgctttgcc atg acc ctg gtc atc ctc ctc gtg gag ctg ggc ggc tcc cag 471
Met Thr Leu Val Ile Leu Leu Val Glu Leu Gly Gly Ser Gln
1 5 10

gcc cgc ttc ccc ttg ttt tgg cgc aac ttc ccc atc acc ttt gcc tgc 519
Ala Arg Phe Pro Leu Phe Trp Arg Asn Phe Pro Ile Thr Phe Ala Cys
15 20 25 30

tat gcg gcc ctc ttg tgc ctc tcg gcc tcc atc atc tac ccc acc acc 567
Tyr Ala Ala Leu Leu Cys Leu Ser Ala Ser Ile Ile Tyr Pro Thr Thr
35 40 45

tac ttg cag ttc ctg tcc cac ggc cgt tcc cgc gac cac gcc atc gcc 615
Tyr Leu Gln Phe Leu Ser His Gly Arg Ser Arg Asp His Ala Ile Ala
50 55 60

gcc atc gtc ttc tct ggc atc gcc tgt gtg gct tac gcc acc gaa gta 663
Ala Ile Val Phe Ser Gly Ile Ala Cys Val Ala Tyr Ala Thr Glu Val
65 70 75

acc tgg acc cgg gcc cgg ccc ggc gag atc act gac tac atg gcc tcc 711
Thr Trp Thr Arg Ala Arg Pro Gly Glu Ile Thr Asp Tyr Met Ala Ser
80 85 90

gag ctg ggg ctg ctg aag gtg ctg gag acc ttc gtg gcc tgc ctc atc 759
Glu Leu Gly Leu Leu Lys Val Leu Glu Thr Phe Val Ala Cys Leu Ile
95 100 105 110

ttc gtg ttc atc aat agc ccc tac gtg tac cac aac cgg ccg gcc ctg 807
Phe Val Phe Ile Asn Ser Pro Tyr Val Tyr His Asn Arg Pro Ala Leu
115 120 125

gag tgg tgg gtg gcg gtg tac gcc ctc tgc ttc gtc ctg gcg gcc ctc 855
Glu Trp Trp Val Ala Val Tyr Ala Leu Cys Phe Val Leu Ala Ala Leu
130 135 140

act atc ctg ctg agc ctg ggg cac tgc acc aac atg ctg ccc atc cgc 903
Thr Ile Leu Leu Ser Leu Gly His Cys Thr Asn Met Leu Pro Ile Arg
145 150 155

ttc ccc agt ttc ctg ttg ggg ctg gcc ttg ctg tcc gtc ctc ctc tat 951
Phe Pro Ser Phe Leu Leu Gly Leu Ala Leu Leu Ser Val Leu Leu Tyr
160 165 170

gcc act gcc ctt gtc ctc tgg ccc ctc tac cag ttc aac gag aag tat 999
Ala Thr Ala Leu Val Leu Trp Pro Leu Tyr Gln Phe Asn Glu Lys Tyr
175 180 185 190

ggt gtc cag ccc tgg cag acg aga gat gtg agc tgc agc gac aga aac 1047
Gly Val Gln Pro Trp Gln Thr Arg Asp Val Ser Cys Ser Asp Arg Asn
195 200 205

ccc tac ctt gtg tgt atc tgg gac cgc cga ctg gct gtg acc aac ctg 1095
Pro Tyr Leu Val Cys Ile Trp Asp Arg Arg Leu Ala Val Thr Asn Leu
210 215 220

acg gcc gtc aac ttg ctg gcc tat gtg ggc gac ctg gtg tac tct gcc 1143

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Thr Ala Val Asn Leu Leu Ala Tyr Val Gly Asp Leu Val Tyr Ser Ala
225 230 235

cac ctg gtt ttt gtc aag gtc taagactccc aaagggcccc gtttgcctct 1194
His Leu Val Phe Val Lys Val
240 245

ccaacctctt catcctgccc ccgctgagtt ttctttattg agtattcatt tcctgggttt 1254

tcctcttccc tatctcccct cctccccttt tctttccttc ccaattcatc gcactttccc 1314

agttctctga tgtatgttct tccctttcct ctgctgtttc cttcttgttt tgttctgttg 1374

cccacaacct gttttcaccc gtttctcttt ttccactctc tcttttgttt ctttcctctc 1434

aattcttttc taggtttcct gttggttttc ttatctgcct atttcccgac catcttctcc 1494

tatttcctgg ggagccctga ggcttttctt ctcctgcccc caagcacctc cagcggtgat 1554

gagctccaca cccccacacc cattgcagct gtggcgccac gtcctcccaa ggggccttct 1614

gcccgccccc gccctagctg tgccttagtc agtgtgtact tgtgtgtgtt tgggggagtg 1674

ggaattgggc ccccttctc ccagtggagg aaggtgtgct gtgcacctcc cctttaaatt 1734

aaaaaaaatg tatgtatctc tggaagtcaa taatttccag tgagcgggag gcttcaagcg 1794

cagaccctgg gtccctagac ctcgcctagc actctgcctt gccagagatt ggctccagaa 1854

tttgtgccag acttacagaa aacccactgc ctagaggcca tcttaaagga agcaatggat 1914

ggatcccttt catcccaact gttcttcgcg gtatc 1949

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<400> 227

Met Thr Leu Val Ile Leu Leu Val Glu Leu Gly Gly Ser Gln Ala Arg
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Phe Pro Leu Phe Trp Arg Asn Phe Pro Ile Thr Phe Ala Cys Tyr Ala
20 25 30

Ala Leu Leu Cys Leu Ser Ala Ser Ile Ile Tyr Pro Thr Thr Tyr Leu
35 40 45

Gln Phe Leu Ser His Gly Arg Ser Arg Asp His Ala Ile Ala Ala Ile
50 55 60

Val Phe Ser Gly Ile Ala Cys Val Ala Tyr Ala Thr Glu Val Thr Trp
65 70 75 80

Thr Arg Ala Arg Pro Gly Glu Ile Thr Asp Tyr Met Ala Ser Glu Leu
85 90 95

Gly Leu Leu Lys Val Leu Glu Thr Phe Val Ala Cys Leu Ile Phe Val
100 105 110

Phe Ile Asn Ser Pro Tyr Val Tyr His Asn Arg Pro Ala Leu Glu Trp
115 120 125

Trp Val Ala Val Tyr Ala Leu Cys Phe Val Leu Ala Ala Leu Thr Ile
130 135 140

Leu Leu Ser Leu Gly His Cys Thr Asn Met Leu Pro Ile Arg Phe Pro
145 150 155 160

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Ser Phe Leu Leu Gly Leu Ala Leu Leu Ser Val Leu Leu Tyr Ala Thr
                165                 170                 175

Ala Leu Val Leu Trp Pro Leu Tyr Gln Phe Asn Glu Lys Tyr Gly Val
            180                 185                 190

Gln Pro Trp Gln Thr Arg Asp Val Ser Cys Ser Asp Arg Asn Pro Tyr
        195                 200                 205

Leu Val Cys Ile Trp Asp Arg Arg Leu Ala Val Thr Asn Leu Thr Ala
    210                 215                 220

Val Asn Leu Leu Ala Tyr Val Gly Asp Leu Val Tyr Ser Ala His Leu
225                 230                 235                 240

Val Phe Val Lys Val
                245
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cagacttgga ggactccagg ccagagacta ggctgggcga agagtcgagc gtgaaggggg     120

ctccgggcca gggtgacagg aggcgtgctt gagaggaaga agttgacggg aaggccagtg     180

cgacggcaaa tctcgtgaac cttgggggac ga atg ctc agg atg cgg gtc ccc       233
                                     Met Leu Arg Met Arg Val Pro
                                     1               5

gcc ctc ctc gtc ctc ctc ttc tgc ttc aga ggg aga gca ggc ccg tcg       281
Ala Leu Leu Val Leu Leu Phe Cys Phe Arg Gly Arg Ala Gly Pro Ser
        10                  15                  20

ccc cat ttc ctg caa cag cca gag gac ctg gtg gtg ctg ctg ggg gag       329
Pro His Phe Leu Gln Gln Pro Glu Asp Leu Val Val Leu Leu Gly Glu
    25                  30                  35

gaa gcc cgg ctg ccg tgt gct ctg ggc gcc tac tgg ggg cta gtt cag       377
Glu Ala Arg Leu Pro Cys Ala Leu Gly Ala Tyr Trp Gly Leu Val Gln
40                  45                  50                  55

tgg act aag agt ggg ctg gcc cta ggg ggc caa agg gac cta cca ggg       425
Trp Thr Lys Ser Gly Leu Ala Leu Gly Gly Gln Arg Asp Leu Pro Gly
                60                  65                  70

tgg tcc cgg tac tgg ata tca ggg aat gca gcc aat ggc cag cat gac       473
Trp Ser Arg Tyr Trp Ile Ser Gly Asn Ala Ala Asn Gly Gln His Asp
            75                  80                  85

ctc cac att agg ccc gtg gag cta gag gat gaa gca tca tat gaa tgt       521
Leu His Ile Arg Pro Val Glu Leu Glu Asp Glu Ala Ser Tyr Glu Cys
        90                  95                  100

cag gct aca caa gca ggc ctc cgc tcc aga cca gcc caa ctg cac gtg       569
Gln Ala Thr Gln Ala Gly Leu Arg Ser Arg Pro Ala Gln Leu His Val
    105                 110                 115

ctg gtc ccc cca gaa gcc ccc cag gtg ctg ggc ggc ccc tct gtg tct       617
Leu Val Pro Pro Glu Ala Pro Gln Val Leu Gly Gly Pro Ser Val Ser
120                 125                 130                 135
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160 200 PCT FINAL.ST25

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ctg gtt gct gga gtt cct gcg aac ctg aca tgt cgg agc cgt ggg gat      665
Leu Val Ala Gly Val Pro Ala Asn Leu Thr Cys Arg Ser Arg Gly Asp
                140                 145                 150

gcc cgc cct acc cct gaa ttg ctg tgg ttc cga gat ggg gtc ctg ttg      713
Ala Arg Pro Thr Pro Glu Leu Leu Trp Phe Arg Asp Gly Val Leu Leu
            155                 160                 165

gat gga gcc acc ttc cat cag acc ctg ctg aag gaa ggg acc cct ggg      761
Asp Gly Ala Thr Phe His Gln Thr Leu Leu Lys Glu Gly Thr Pro Gly
        170                 175                 180

tca gtg gag agc acc tta acc ctg acc cct ttc agc cat gat gat gga      809
Ser Val Glu Ser Thr Leu Thr Leu Thr Pro Phe Ser His Asp Asp Gly
    185                 190                 195

gcc acc ttt gtc tgc cgg gcc cgg agc cag gcc ctg ccc aca gga aga      857
Ala Thr Phe Val Cys Arg Ala Arg Ser Gln Ala Leu Pro Thr Gly Arg
200                 205                 210                 215

gac aca gct atc aca ctg agc ctg cag tac ccc cca gag gtg act ctg      905
Asp Thr Ala Ile Thr Leu Ser Leu Gln Tyr Pro Pro Glu Val Thr Leu
                220                 225                 230

tct gct tcg cca cac act gtg cag gag gga gag aag gtc att ttc ctg      953
Ser Ala Ser Pro His Thr Val Gln Glu Gly Glu Lys Val Ile Phe Leu
            235                 240                 245

tgc cag gcc aca gcc cag cct cct gtc aca ggc tac agg tgg gca aaa     1001
Cys Gln Ala Thr Ala Gln Pro Pro Val Thr Gly Tyr Arg Trp Ala Lys
        250                 255                 260

ggg ggc tct ccg gtg ctc ggg gcc cgc ggg cca agg tta gag gtc gtg     1049
Gly Gly Ser Pro Val Leu Gly Ala Arg Gly Pro Arg Leu Glu Val Val
    265                 270                 275

gca gac gcc tcg ttc ctg act gag ccc gtg tcc tgc gag gtc agc aac     1097
Ala Asp Ala Ser Phe Leu Thr Glu Pro Val Ser Cys Glu Val Ser Asn
280                 285                 290                 295

gcc gtg ggt agc gcc aac cgc agt act gcg ctg gat gtg ctg ttt ggg     1145
Ala Val Gly Ser Ala Asn Arg Ser Thr Ala Leu Asp Val Leu Phe Gly
                300                 305                 310

ccg att ctg cag gca aag ccg gag ccc gtg tcc gtg gac gtg ggg gaa     1193
Pro Ile Leu Gln Ala Lys Pro Glu Pro Val Ser Val Asp Val Gly Glu
            315                 320                 325

gac gct tcc ttc agc tgc gcc tgg cgc ggg aac ccg ctt cca cgg gta     1241
Asp Ala Ser Phe Ser Cys Ala Trp Arg Gly Asn Pro Leu Pro Arg Val
        330                 335                 340

acc tgg acc cgc cgc ggt ggc gcg cag gtg ctg ggc tct gga gcc aca     1289
Thr Trp Thr Arg Arg Gly Gly Ala Gln Val Leu Gly Ser Gly Ala Thr
    345                 350                 355

ctg cgt ctt ccg tcg gtg ggg ccc gag gac gca ggc gac tat gtg tgc     1337
Leu Arg Leu Pro Ser Val Gly Pro Glu Asp Ala Gly Asp Tyr Val Cys
360                 365                 370                 375

aga gct gag gct ggg cta tcg ggc ctg cgg ggc ggc gcc gcg gag gct     1385
Arg Ala Glu Ala Gly Leu Ser Gly Leu Arg Gly Gly Ala Ala Glu Ala
                380                 385                 390

cgg ctg act gtg aac gct ccc cca gta gtg acc gcc ctg cac tct gcg     1433
Arg Leu Thr Val Asn Ala Pro Pro Val Val Thr Ala Leu His Ser Ala
            395                 400                 405

cct gcc ttc ctg agg ggc cct gct cgc ctc cag tgt ctg gtt ttc gcc     1481
Pro Ala Phe Leu Arg Gly Pro Ala Arg Leu Gln Cys Leu Val Phe Ala
        410                 415                 420

tct ccc gcc cca gat gcc gtg gtc tgg tct tgg gat gag ggc ttc ctg     1529
Ser Pro Ala Pro Asp Ala Val Val Trp Ser Trp Asp Glu Gly Phe Leu
    425                 430                 435

gag gcg ggg tcg cag ggc cgg ttc ctg gtg gag aca ttc cct gcc cca     1577
Glu Ala Gly Ser Gln Gly Arg Phe Leu Val Glu Thr Phe Pro Ala Pro
440                 445                 450                 455
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Glu Ser Arg Gly Gly Leu Gly Pro Gly Leu Ile Ser Val Leu His Ile
                460                 465                 470

tcg ggg acc cag gag tct gac ttt agc agg agc ttt aac tgc agt gcc     1673
Ser Gly Thr Gln Glu Ser Asp Phe Ser Arg Ser Phe Asn Cys Ser Ala
            475                 480                 485

cgg aac cgg ctg ggc gag gga ggt gcc cag gcc agc ctg ggc cgt aga     1721
Arg Asn Arg Leu Gly Glu Gly Gly Ala Gln Ala Ser Leu Gly Arg Arg
        490                 495                 500

gac ttg ctg ccc act gtg cgg ata gtg gcc gga gtg gcc gct gcc acc     1769
Asp Leu Leu Pro Thr Val Arg Ile Val Ala Gly Val Ala Ala Ala Thr
    505                 510                 515

aca act ctc ctt atg gtc atc act ggg gtg gcc ctc tgc tgc tgg cgc     1817
Thr Thr Leu Leu Met Val Ile Thr Gly Val Ala Leu Cys Cys Trp Arg
520                 525                 530                 535

cac agc aag gcc tca gcc tct ttc tcc gag caa aag aac ctg atg cga     1865
His Ser Lys Ala Ser Ala Ser Phe Ser Glu Gln Lys Asn Leu Met Arg
                540                 545                 550

atc cct ggc agc agc gac ggc tcc agt tca cga ggt cct gaa gaa gag     1913
Ile Pro Gly Ser Ser Asp Gly Ser Ser Ser Arg Gly Pro Glu Glu Glu
            555                 560                 565

gag aca ggc agc cgc gag gac cgg ggc ccc att gtg cac act gac cac     1961
Glu Thr Gly Ser Arg Glu Asp Arg Gly Pro Ile Val His Thr Asp His
        570                 575                 580

agt gat ctg gtt ctg gag gag aaa ggg act ctg gag acc aag gac cca     2009
Ser Asp Leu Val Leu Glu Glu Lys Gly Thr Leu Glu Thr Lys Asp Pro
    585                 590                 595

acc aac ggt tac tac aag gtc cga gga gtc agt gtg agc ctg agc ctt     2057
Thr Asn Gly Tyr Tyr Lys Val Arg Gly Val Ser Val Ser Leu Ser Leu
600                 605                 610                 615

ggc gaa gcc cct gga gga ggt ctc ttc ctg cca cca ccc tcc ccc ctt     2105
Gly Glu Ala Pro Gly Gly Gly Leu Phe Leu Pro Pro Pro Ser Pro Leu
                620                 625                 630

ggg ccc cca ggg acc cct acc ttc tat gac ttc aac cca cac ctg ggc     2153
Gly Pro Pro Gly Thr Pro Thr Phe Tyr Asp Phe Asn Pro His Leu Gly
            635                 640                 645

atg gtc ccc ccc tgc aga ctt tac aga gcc agg gca ggc tat ctc acc     2201
Met Val Pro Pro Cys Arg Leu Tyr Arg Ala Arg Ala Gly Tyr Leu Thr
        650                 655                 660

aca ccc cac cct cga gct ttc acc agc tac atc aaa ccc aca tcc ttt     2249
Thr Pro His Pro Arg Ala Phe Thr Ser Tyr Ile Lys Pro Thr Ser Phe
    665                 670                 675

ggg ccc cca gat ctg gcc ccc ggg act ccc ccc ttc cca tat gct gcc     2297
Gly Pro Pro Asp Leu Ala Pro Gly Thr Pro Pro Phe Pro Tyr Ala Ala
680                 685                 690                 695

ttc ccc aca cct agc cac ccg cgt ctc cag act cac gtg tgacatcttt     2346
Phe Pro Thr Pro Ser His Pro Arg Leu Gln Thr His Val
                700                 705

ccaatggaag agtcctggga tctccaactt gccataatgg attgttctga tttctgagga   2406

gccaggacaa gttggcgacc ttactcctcc aaaactgaac acaaggggag ggaaagatca   2466

ttacatttgt caggagcatt tgtatacagt cagctcagcc aaaggagatg ccccaagtgg   2526

gagcaacatg gccacccaat atgcccacct attccccggt gtaaaagaga ttcaagatgg   2586

caggtaggcc ctttgaggag agatggggac agggcagtgg gtgttgggag tttggggccg   2646

ggatggaagt tgtttctagc cactgaaaga agatatttca agatgaccat ctgcattgag   2706

aggaaaggta gcataggata gatgaagatg aagagcatac caggccccac cctggctctc   2766
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gaacccaaga tggccaccat cttgatttta ctttccttaa agactcagaa agacttggac 2886

ccaaggagtg gggatacagt gagaattacc actgttgggg caaaatattg ggataaaaat 2946

atttatgttt aataataaaa aaaagtcaaa gagg 2980

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20 25 30

Leu Val Val Leu Leu Gly Glu Glu Ala Arg Leu Pro Cys Ala Leu Gly
35 40 45

Ala Tyr Trp Gly Leu Val Gln Trp Thr Lys Ser Gly Leu Ala Leu Gly
50 55 60

Gly Gln Arg Asp Leu Pro Gly Trp Ser Arg Tyr Trp Ile Ser Gly Asn
65 70 75 80

Ala Ala Asn Gly Gln His Asp Leu His Ile Arg Pro Val Glu Leu Glu
85 90 95

Asp Glu Ala Ser Tyr Glu Cys Gln Ala Thr Gln Ala Gly Leu Arg Ser
100 105 110

Arg Pro Ala Gln Leu His Val Leu Val Pro Pro Glu Ala Pro Gln Val
115 120 125

Leu Gly Gly Pro Ser Val Ser Leu Val Ala Gly Val Pro Ala Asn Leu
130 135 140

Thr Cys Arg Ser Arg Gly Asp Ala Arg Pro Thr Pro Glu Leu Leu Trp
145 150 155 160

Phe Arg Asp Gly Val Leu Leu Asp Gly Ala Thr Phe His Gln Thr Leu
165 170 175

Leu Lys Glu Gly Thr Pro Gly Ser Val Glu Ser Thr Leu Thr Leu Thr
180 185 190

Pro Phe Ser His Asp Asp Gly Ala Thr Phe Val Cys Arg Ala Arg Ser
195 200 205

Gln Ala Leu Pro Thr Gly Arg Asp Thr Ala Ile Thr Leu Ser Leu Gln
210 215 220

Tyr Pro Pro Glu Val Thr Leu Ser Ala Ser Pro His Thr Val Gln Glu
225 230 235 240

Gly Glu Lys Val Ile Phe Leu Cys Gln Ala Thr Ala Gln Pro Pro Val
245 250 255

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Thr Gly Tyr Arg Trp Ala Lys Gly Gly Ser Pro Val Leu Gly Ala Arg
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Gly Pro Arg Leu Glu Val Val Ala Asp Ala Ser Phe Leu Thr Glu Pro
275 280 285

Val Ser Cys Glu Val Ser Asn Ala Val Gly Ser Ala Asn Arg Ser Thr
290 295 300

Ala Leu Asp Val Leu Phe Gly Pro Ile Leu Gln Ala Lys Pro Glu Pro
305 310 315 320

Val Ser Val Asp Val Gly Glu Asp Ala Ser Phe Ser Cys Ala Trp Arg
325 330 335

Gly Asn Pro Leu Pro Arg Val Thr Trp Thr Arg Arg Gly Gly Ala Gln
340 345 350

Val Leu Gly Ser Gly Ala Thr Leu Arg Leu Pro Ser Val Gly Pro Glu
355 360 365

Asp Ala Gly Asp Tyr Val Cys Arg Ala Glu Ala Gly Leu Ser Gly Leu
370 375 380

Arg Gly Gly Ala Ala Glu Ala Arg Leu Thr Val Asn Ala Pro Pro Val
385 390 395 400

Val Thr Ala Leu His Ser Ala Pro Ala Phe Leu Arg Gly Pro Ala Arg
405 410 415

Leu Gln Cys Leu Val Phe Ala Ser Pro Ala Pro Asp Ala Val Val Trp
420 425 430

Ser Trp Asp Glu Gly Phe Leu Glu Ala Gly Ser Gln Gly Arg Phe Leu
435 440 445

Val Glu Thr Phe Pro Ala Pro Glu Ser Arg Gly Gly Leu Gly Pro Gly
450 455 460

Leu Ile Ser Val Leu His Ile Ser Gly Thr Gln Glu Ser Asp Phe Ser
465 470 475 480

Arg Ser Phe Asn Cys Ser Ala Arg Asn Arg Leu Gly Glu Gly Gly Ala
485 490 495

Gln Ala Ser Leu Gly Arg Arg Asp Leu Leu Pro Thr Val Arg Ile Val
500 505 510

Ala Gly Val Ala Ala Ala Thr Thr Thr Leu Leu Met Val Ile Thr Gly
515 520 525

Val Ala Leu Cys Cys Trp Arg His Ser Lys Ala Ser Ala Ser Phe Ser
530 535 540

Glu Gln Lys Asn Leu Met Arg Ile Pro Gly Ser Ser Asp Gly Ser Ser
545 550 555 560

Ser Arg Gly Pro Glu Glu Glu Glu Thr Gly Ser Arg Glu Asp Arg Gly
565 570 575

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Pro Ile Val His Thr Asp His Ser Asp Leu Val Leu Glu Glu Lys Gly
580 585 590

Thr Leu Glu Thr Lys Asp Pro Thr Asn Gly Tyr Tyr Lys Val Arg Gly
595 600 605

Val Ser Val Ser Leu Ser Leu Gly Glu Ala Pro Gly Gly Gly Leu Phe
610 615 620

Leu Pro Pro Pro Ser Pro Leu Gly Pro Pro Gly Thr Pro Thr Phe Tyr
625 630 635 640

Asp Phe Asn Pro His Leu Gly Met Val Pro Pro Cys Arg Leu Tyr Arg
645 650 655

Ala Arg Ala Gly Tyr Leu Thr Thr Pro His Pro Arg Ala Phe Thr Ser
660 665 670

Tyr Ile Lys Pro Thr Ser Phe Gly Pro Pro Asp Leu Ala Pro Gly Thr
675 680 685

Pro Pro Phe Pro Tyr Ala Ala Phe Pro Thr Pro Ser His Pro Arg Leu
690 695 700

Gln Thr His Val
705

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gagcacagaa aagaaaaaaa aaagccttaa gaggaccgaa ggggaggaaa ggaaaaggat 180

ggacaaccac aaaacgcagc gattgcggaa attttccagc gccattggct gggcagcgtg 240

agtccttcgg tcgggcgtga tttcagcacc gggggaactg gacagcacct cgggggggact 300

tctgggcaac ccgcaaccac agcaagaact ccaccagcag cctcaacaac agaagccgcg 360

gaaaaccctg ctttgtatca gagaggcaag gtcagtccga cgcacagcca tgcacaggca 420

gtgcgcctgt actacgctgc aaaccctctg cttgtttctc taacatgcac ttgcttctaa 480

ttactagcat tgtttcattt ctgatcagtg aagatcagta gatgagattc tgtaagggtg 540

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gggagtgggg ttttttttcct actttttttt ttttttttt ttctttgctt gccttgcact 660

acgtgcctgg atagtttgtg gatataatta ttgactggcg tctgggctat tgcagtgcgg 720

gggggttagg gaggaaggaa tccacccccа cccccccaaa ccctttttctt ctcctttcct 780

ggcttcggac attggagcac taaatgaact tgaattgtgt ctgtggcgag caggatggtc 840

gctgttactt tgtgatgaga tcggggatga attgctcgct ttaaaa atg ctg ctt 895
Met Leu Leu

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Trp Ile Leu Leu Leu Glu Thr Ser Leu Cys Phe Ala Ala Gly Asn Val
    5                  10                  15

aca ggg gac gtt tgc aaa gag aag atc tgt tcc tgc aat gag ata gaa      991
Thr Gly Asp Val Cys Lys Glu Lys Ile Cys Ser Cys Asn Glu Ile Glu
20                  25                  30                  35

ggg gac cta cac gta gac tgt gaa aaa aag ggc ttc aca agt ctg cag     1039
Gly Asp Leu His Val Asp Cys Glu Lys Lys Gly Phe Thr Ser Leu Gln
                40                  45                  50

cgt ttc act gcc ccg act tcc cag ttt tac cat tta ttt ctg cat ggc     1087
Arg Phe Thr Ala Pro Thr Ser Gln Phe Tyr His Leu Phe Leu His Gly
            55                  60                  65

aat tcc ctc act cga ctt ttc cct aat gag ttc gct aac ttt tat aat     1135
Asn Ser Leu Thr Arg Leu Phe Pro Asn Glu Phe Ala Asn Phe Tyr Asn
        70                  75                  80

gcg gtt agt ttg cac atg gaa aac aat ggc ttg cat gaa atc gtt ccg     1183
Ala Val Ser Leu His Met Glu Asn Asn Gly Leu His Glu Ile Val Pro
    85                  90                  95

ggg gct ttt ctg ggg ctg cag ctg gtg aaa agg ctg cac atc aac aac     1231
Gly Ala Phe Leu Gly Leu Gln Leu Val Lys Arg Leu His Ile Asn Asn
100                 105                 110                 115

aac aag atc aag tct ttt cga aag cag act ttt ctg ggg ctg gac gat     1279
Asn Lys Ile Lys Ser Phe Arg Lys Gln Thr Phe Leu Gly Leu Asp Asp
                120                 125                 130

ctg gaa tat ctc cag gct gat ttt aat tta tta cga gat ata gac ccg     1327
Leu Glu Tyr Leu Gln Ala Asp Phe Asn Leu Leu Arg Asp Ile Asp Pro
            135                 140                 145

ggg gcc ttc cag gac ttg aac aag ctg gag gtg ctc att tta aat gac     1375
Gly Ala Phe Gln Asp Leu Asn Lys Leu Glu Val Leu Ile Leu Asn Asp
        150                 155                 160

aat ctc atc agc acc cta cct gcc aac gtg ttc cag tat gtg ccc atc     1423
Asn Leu Ile Ser Thr Leu Pro Ala Asn Val Phe Gln Tyr Val Pro Ile
    165                 170                 175

acc cac ctc gac ctc cgg ggt aac agg ctg aaa acg ctg ccc tat gag     1471
Thr His Leu Asp Leu Arg Gly Asn Arg Leu Lys Thr Leu Pro Tyr Glu
180                 185                 190                 195

gag gtc ttg gag caa atc cct ggt att gcg gag atc ctg cta gag gat     1519
Glu Val Leu Glu Gln Ile Pro Gly Ile Ala Glu Ile Leu Leu Glu Asp
                200                 205                 210

aac cct tgg gac tgc acc tgt gat ctg ctc tcc ctg aaa gaa tgg ctg     1567
Asn Pro Trp Asp Cys Thr Cys Asp Leu Leu Ser Leu Lys Glu Trp Leu
            215                 220                 225

gaa aac att ccc aag aat gcc ctg atc ggc cga gtg gtc tgc gaa gcc     1615
Glu Asn Ile Pro Lys Asn Ala Leu Ile Gly Arg Val Val Cys Glu Ala
        230                 235                 240

ccc acc aga ctg cag ggt aaa gac ctc aat gaa acc acc gaa cag gac     1663
Pro Thr Arg Leu Gln Gly Lys Asp Leu Asn Glu Thr Thr Glu Gln Asp
    245                 250                 255

ttg tgt cct ttg aaa aac cga gtg gat tct agt ctc ccg gcg ccc cct     1711
Leu Cys Pro Leu Lys Asn Arg Val Asp Ser Ser Leu Pro Ala Pro Pro
260                 265                 270                 275

gcc caa gaa gag acc ttt gct cct gga ccc ctg cca act cct ttc aag     1759
Ala Gln Glu Glu Thr Phe Ala Pro Gly Pro Leu Pro Thr Pro Phe Lys
                280                 285                 290

aca aat ggg caa gag gat cat gcc aca cca ggg tct gct cca aac gga     1807
Thr Asn Gly Gln Glu Asp His Ala Thr Pro Gly Ser Ala Pro Asn Gly
            295                 300                 305

ggt aca aag atc cca ggc aac tgg cag atc aaa atc aga ccc aca gca     1855
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Gly Thr Lys Ile Pro Gly Asn Trp Gln Ile Lys Ile Arg Pro Thr Ala
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gcg ata gcg acg ggt agc tcc agg aac aaa ccc tta gct aac agt tta     1903
Ala Ile Ala Thr Gly Ser Ser Arg Asn Lys Pro Leu Ala Asn Ser Leu
    325                 330                 335

ccc tgc cct ggg ggc tgc agc tgc gac cac atc cca ggg tcg ggt tta     1951
Pro Cys Pro Gly Gly Cys Ser Cys Asp His Ile Pro Gly Ser Gly Leu
340                 345                 350                 355

aag atg aac tgc aac aac agg aac gtg agc agc ttg gct gat ttg aag     1999
Lys Met Asn Cys Asn Asn Arg Asn Val Ser Ser Leu Ala Asp Leu Lys
                360                 365                 370

ccc aag ctc tct aac gtg cag gag ctt ttc cta cga gat aac aag atc     2047
Pro Lys Leu Ser Asn Val Gln Glu Leu Phe Leu Arg Asp Asn Lys Ile
            375                 380                 385

cac agc atc cga aaa tcg cac ttt gtg gat tac aag aac ctc att ctg     2095
His Ser Ile Arg Lys Ser His Phe Val Asp Tyr Lys Asn Leu Ile Leu
        390                 395                 400

ttg gat ctg ggc aac aat aac atc gct act gta gag aac aac act ttc     2143
Leu Asp Leu Gly Asn Asn Asn Ile Ala Thr Val Glu Asn Asn Thr Phe
    405                 410                 415

aag aac ctt ttg gac ctc agg tgg cta tac atg gat agc aat tac ctg     2191
Lys Asn Leu Leu Asp Leu Arg Trp Leu Tyr Met Asp Ser Asn Tyr Leu
420                 425                 430                 435

gac acg ctg tcc cgg gag aaa ttc gcg ggg ctg caa aac cta gag tac     2239
Asp Thr Leu Ser Arg Glu Lys Phe Ala Gly Leu Gln Asn Leu Glu Tyr
                440                 445                 450

ctg aac gtg gag tac aac gct atc cag ctc atc ctc ccg ggc act ttc     2287
Leu Asn Val Glu Tyr Asn Ala Ile Gln Leu Ile Leu Pro Gly Thr Phe
            455                 460                 465

aat gcc atg ccc aaa ctg agg atc ctc att ctc aac aac aac ctg ctg     2335
Asn Ala Met Pro Lys Leu Arg Ile Leu Ile Leu Asn Asn Asn Leu Leu
        470                 475                 480

agg tcc ctg cct gtg gac gtg ttc gct ggg gtc tcg ctc tct aaa ctc     2383
Arg Ser Leu Pro Val Asp Val Phe Ala Gly Val Ser Leu Ser Lys Leu
    485                 490                 495

agc ctg cac aac aat tac ttc atg tac ctc ccg gtg gca ggg gtg ctg     2431
Ser Leu His Asn Asn Tyr Phe Met Tyr Leu Pro Val Ala Gly Val Leu
500                 505                 510                 515

gac cag tta acc tcc atc atc cag ata gac ctc cac gga aac ccc tgg     2479
Asp Gln Leu Thr Ser Ile Ile Gln Ile Asp Leu His Gly Asn Pro Trp
                520                 525                 530

gag tgc tcc tgc aca att gtg cct ttc aag cag tgg gca gaa cgc ttg     2527
Glu Cys Ser Cys Thr Ile Val Pro Phe Lys Gln Trp Ala Glu Arg Leu
            535                 540                 545

ggt tcc gaa gtg ctg atg agc gac ctc aag tgt gag acg ccg gtg aac     2575
Gly Ser Glu Val Leu Met Ser Asp Leu Lys Cys Glu Thr Pro Val Asn
        550                 555                 560

ttc ttt aga aag gat ttc atg ctc ctc tcc aat gac gag atc tgc cct     2623
Phe Phe Arg Lys Asp Phe Met Leu Leu Ser Asn Asp Glu Ile Cys Pro
    565                 570                 575

cag ctg tac gct agg atc tcg ccc acg tta act tcg cac agt aaa aac     2671
Gln Leu Tyr Ala Arg Ile Ser Pro Thr Leu Thr Ser His Ser Lys Asn
580                 585                 590                 595

agc act ggg ttg gcg gag acc ggg acg cac tcc aac tcc tac cta gac     2719
Ser Thr Gly Leu Ala Glu Thr Gly Thr His Ser Asn Ser Tyr Leu Asp
                600                 605                 610

acc agc agg gtg tcc atc tcg gtg ttg gtc ccg gga ctg ctg ctg gtg     2767
Thr Ser Arg Val Ser Ile Ser Val Leu Val Pro Gly Leu Leu Leu Val
            615                 620                 625
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Phe Val Thr Ser Ala Phe Thr Val Val Gly Met Leu Val Phe Ile Leu
        630                 635                 640

agg aac cga aag cgg tcc aag aga cga gat gcc aac tcc tcc gcg tcc     2863
Arg Asn Arg Lys Arg Ser Lys Arg Arg Asp Ala Asn Ser Ser Ala Ser
    645                 650                 655

gag att aat tcc cta cag aca gtc tgt gac tct tcc tac tgg cac aat     2911
Glu Ile Asn Ser Leu Gln Thr Val Cys Asp Ser Ser Tyr Trp His Asn
660                 665                 670                 675

ggg cct tac aac gca gat ggg gcc cac aga gtg tat gac tgt ggc tct     2959
Gly Pro Tyr Asn Ala Asp Gly Ala His Arg Val Tyr Asp Cys Gly Ser
                680                 685                 690

cac tcg ctc tca gac taagacccca accccaatag gggagggcag agggaaggcg     3014
His Ser Leu Ser Asp
            695

atacatcctt ccccaccgca ggcaccccgg gggctggagg ggcgtgtacc caaatccccg   3074

cgccatcagc ctggatgggc ataagtagat aaataactgt gagctcgcac aaccgaaagg   3134

gcctgacccc ttacttagct ccctccttga aacaaagagc agactgtgga gagctgggag   3194

agcgcagcca gctcgctctt tgctgagagc ccctttgac agaaagccca gcacgaccct    3254

gctggaagaa ctgacagtgc cctcgccctc ggccccgggg cctgtggggt tggatgccgc   3314

ggtttctatac atatatacat atatccacat ctatatagag agatagatat ctatttttcc  3374

cctgtggatt agccccgtga tggctccctg ttggctacgc agggatgggc agttgcacga   3434

aggcatgaat gtattgtaaa taagtaactt tgacttctga caaaaaacaa aaagtgctgc   3494

atggctcgca tggaatccac gcgctccagg gactctgccc gcccccgcga ctggagacgg   3554

catctcgttc acagcaccca ccctcttacc tgataagttc catcgtatca aactttctat   3614

aaacaaaata cagtataatc agaaagtgcc atttcgccat tatttgtgat cggtaggcag   3674

ttcagagcat aagttaactg tgaaaaaaat gtaaaggttt tatttaggac atttgcatgg   3734

ctagtcatca gtccatttta tgagttaaca atgtattttg ttgagggaag tttttagggg   3794

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gtctttttttt taatacatat ccaataatgc cttccatctg aatgtaaaat aagtacccat   3914

gatttctatt atagtatcag tgtaattatt taaaaaatga ttttgaggca gttaagcatg   3974

accaattaat gtcactctag tgcttaggct gcgatcctat ggtagcaatt ctgtgctggt   4034

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ctattcgagg attttataat ggcatatttt ttcagtatta aagcgaaaat gttttcaact   4154

ctgggtcctt accttttttcc agcttcatat ttgcaagtgg taaattggat ttgcggtgga   4214

agagacaggg gagggaaacg gttggggtta gatcccttcc tgagctacat taaggctctt   4274

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cctctacccc accccccacct tcgctcagac tttaccggct ttccccagtc cataaaggtc   4394

ttgccccaac actcaccccct tctttttttc ccctctccaa atgcagcagt gaatcccttt   4454

attaatactg gaaatccctc tctgctgctt ttgttggtgc tgcccacact gcagatatat   4514

taaggatgtt aggagagatt tgatttaatt gactctgcct agataggtct cattaaacag   4574

agtggagatt tcattggtca gcactcctca atgaaagaca gacctaatga ctggcatttg   4634

agatgctgct ggcattttga attcaacatc tgctgaaaac ggtaaaacta attagtgccc   4694

acccaccctc cccgccccag caactgcata ttgaaatttg ttaaagcact catctttatg   4754

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ccacacatat tgatggagtc tgcattccac cacatatcca cccttgagaa gtatgtcaaa 4994

agactgcaga ctatagattt ttttttaata taggattata aatcagctag tgaaagacct 5054

cagagcagtt gtaagtagat ctgccatcta gaactcatat tctaaaggga agtgatttct 5114

cagaacagtg atgttctgga atatgtatta tttatttttaa cacttttttta ataaaatctt 5174

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Gly Asn Val Thr Gly Asp Val Cys Lys Glu Lys Ile Cys Ser Cys Asn
20 25 30

Glu Ile Glu Gly Asp Leu His Val Asp Cys Glu Lys Lys Gly Phe Thr
35 40 45

Ser Leu Gln Arg Phe Thr Ala Pro Thr Ser Gln Phe Tyr His Leu Phe
50 55 60

Leu His Gly Asn Ser Leu Thr Arg Leu Phe Pro Asn Glu Phe Ala Asn
65 70 75 80

Phe Tyr Asn Ala Val Ser Leu His Met Glu Asn Asn Gly Leu His Glu
85 90 95

Ile Val Pro Gly Ala Phe Leu Gly Leu Gln Leu Val Lys Arg Leu His
100 105 110

Ile Asn Asn Asn Lys Ile Lys Ser Phe Arg Lys Gln Thr Phe Leu Gly
115 120 125

Leu Asp Asp Leu Glu Tyr Leu Gln Ala Asp Phe Asn Leu Leu Arg Asp
130 135 140

Ile Asp Pro Gly Ala Phe Gln Asp Leu Asn Lys Leu Glu Val Leu Ile
145 150 155 160

Leu Asn Asp Asn Leu Ile Ser Thr Leu Pro Ala Asn Val Phe Gln Tyr
165 170 175

Val Pro Ile Thr His Leu Asp Leu Arg Gly Asn Arg Leu Lys Thr Leu
180 185 190

Pro Tyr Glu Glu Val Leu Glu Gln Ile Pro Gly Ile Ala Glu Ile Leu
195 200 205

Leu Glu Asp Asn Pro Trp Asp Cys Thr Cys Asp Leu Leu Ser Leu Lys
210 215 220

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Glu Trp Leu Glu Asn Ile Pro Lys Asn Ala Leu Ile Gly Arg Val Val
225 230 235 240

Cys Glu Ala Pro Thr Arg Leu Gln Gly Lys Asp Leu Asn Glu Thr Thr
245 250 255

Glu Gln Asp Leu Cys Pro Leu Lys Asn Arg Val Asp Ser Ser Leu Pro
260 265 270

Ala Pro Pro Ala Gln Glu Glu Thr Phe Ala Pro Gly Pro Leu Pro Thr
275 280 285

Pro Phe Lys Thr Asn Gly Gln Glu Asp His Ala Thr Pro Gly Ser Ala
290 295 300

Pro Asn Gly Gly Thr Lys Ile Pro Gly Asn Trp Gln Ile Lys Ile Arg
305 310 315 320

Pro Thr Ala Ala Ile Ala Thr Gly Ser Ser Arg Asn Lys Pro Leu Ala
325 330 335

Asn Ser Leu Pro Cys Pro Gly Gly Cys Ser Cys Asp His Ile Pro Gly
340 345 350

Ser Gly Leu Lys Met Asn Cys Asn Asn Arg Asn Val Ser Ser Leu Ala
355 360 365

Asp Leu Lys Pro Lys Leu Ser Asn Val Gln Glu Leu Phe Leu Arg Asp
370 375 380

Asn Lys Ile His Ser Ile Arg Lys Ser His Phe Val Asp Tyr Lys Asn
385 390 395 400

Leu Ile Leu Leu Asp Leu Gly Asn Asn Asn Ile Ala Thr Val Glu Asn
405 410 415

Asn Thr Phe Lys Asn Leu Leu Asp Leu Arg Trp Leu Tyr Met Asp Ser
420 425 430

Asn Tyr Leu Asp Thr Leu Ser Arg Glu Lys Phe Ala Gly Leu Gln Asn
435 440 445

Leu Glu Tyr Leu Asn Val Glu Tyr Asn Ala Ile Gln Leu Ile Leu Pro
450 455 460

Gly Thr Phe Asn Ala Met Pro Lys Leu Arg Ile Leu Ile Leu Asn Asn
465 470 475 480

Asn Leu Leu Arg Ser Leu Pro Val Asp Val Phe Ala Gly Val Ser Leu
485 490 495

Ser Lys Leu Ser Leu His Asn Asn Tyr Phe Met Tyr Leu Pro Val Ala
500 505 510

Gly Val Leu Asp Gln Leu Thr Ser Ile Ile Gln Ile Asp Leu His Gly
515 520 525

Asn Pro Trp Glu Cys Ser Cys Thr Ile Val Pro Phe Lys Gln Trp Ala
530 535 540

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Glu Arg Leu Gly Ser Glu Val Leu Met Ser Asp Leu Lys Cys Glu Thr
545                 550                 555                 560

Pro Val Asn Phe Phe Arg Lys Asp Phe Met Leu Leu Ser Asn Asp Glu
                565                 570                 575

Ile Cys Pro Gln Leu Tyr Ala Arg Ile Ser Pro Thr Leu Thr Ser His
            580                 585                 590

Ser Lys Asn Ser Thr Gly Leu Ala Glu Thr Gly Thr His Ser Asn Ser
        595                 600                 605

Tyr Leu Asp Thr Ser Arg Val Ser Ile Ser Val Leu Val Pro Gly Leu
    610                 615                 620

Leu Leu Val Phe Val Thr Ser Ala Phe Thr Val Val Gly Met Leu Val
625                 630                 635                 640

Phe Ile Leu Arg Asn Arg Lys Arg Ser Lys Arg Arg Asp Ala Asn Ser
                645                 650                 655

Ser Ala Ser Glu Ile Asn Ser Leu Gln Thr Val Cys Asp Ser Ser Tyr
            660                 665                 670

Trp His Asn Gly Pro Tyr Asn Ala Asp Gly Ala His Arg Val Tyr Asp
        675                 680                 685

Cys Gly Ser His Ser Leu Ser Asp
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                                  1               5

agg acg aag atc atg atc ggc atc gga agc agc tta ctg gtt gcc gcg      100
Arg Thr Lys Ile Met Ile Gly Ile Gly Ser Ser Leu Leu Val Ala Ala
        10                  15                  20

atg gtg ctc cta agt gtt gtg ttc tgt ctt tac ttc aaa gta gct aag      148
Met Val Leu Leu Ser Val Val Phe Cys Leu Tyr Phe Lys Val Ala Lys
    25                  30                  35

gca cta aaa gct gca aag gac cct gat gct gtg gct gta aaa aat cac      196
Ala Leu Lys Ala Ala Lys Asp Pro Asp Ala Val Ala Val Lys Asn His
40                  45                  50                  55

aac cca gac aag gtg tgt tgg gcc acg aac agc cag gcc aaa gcc acc      244
Asn Pro Asp Lys Val Cys Trp Ala Thr Asn Ser Gln Ala Lys Ala Thr
                60                  65                  70

acc atg gag tct tgt cca tct ctc cag tgc tgt gaa ggt tgt aga atg      292
Thr Met Glu Ser Cys Pro Ser Leu Gln Cys Cys Glu Gly Cys Arg Met
            75                  80                  85

cat gcc agt tct gat tcc ctg cca cct tgc tgt tgt gac ata aat gag      340
His Ala Ser Ser Asp Ser Leu Pro Pro Cys Cys Cys Asp Ile Asn Glu
        90                  95                  100
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Gly Leu
105

taatagaatg ttttattatt caagtcaagt tctagagtgt ttacatacta ttatataatg 456

tacagtgtta ttttctgtac ttctgaataa atgtgcaata ttggaaataa 506

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<400> 233

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Ser Ser Leu Leu Val Ala Ala Met Val Leu Leu Ser Val Val Phe Cys
20 25 30

Leu Tyr Phe Lys Val Ala Lys Ala Leu Lys Ala Ala Lys Asp Pro Asp
35 40 45

Ala Val Ala Val Lys Asn His Asn Pro Asp Lys Val Cys Trp Ala Thr
50 55 60

Asn Ser Gln Ala Lys Ala Thr Thr Met Glu Ser Cys Pro Ser Leu Gln
65 70 75 80

Cys Cys Glu Gly Cys Arg Met His Ala Ser Ser Asp Ser Leu Pro Pro
85 90 95

Cys Cys Cys Asp Ile Asn Glu Gly Leu
100 105

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ttaccatact tactggcctt ggctggctct tcagctcttg gatccttaat cgaggaagc 179

atg acc acc aac ttg gat ctg aag gta tcc atg ctc agc ttc atc tca 227
Met Thr Thr Asn Leu Asp Leu Lys Val Ser Met Leu Ser Phe Ile Ser
1 5 10 15

gct acc tgc ttg ctc ctc tgc ctc aac ctg ttt gtg gca cag gtt cac 275
Ala Thr Cys Leu Leu Leu Cys Leu Asn Leu Phe Val Ala Gln Val His
20 25 30

tgg cat act agg gat gcc atg gag tca gat ctc cta tgg acc tat tat 323
Trp His Thr Arg Asp Ala Met Glu Ser Asp Leu Leu Trp Thr Tyr Tyr
35 40 45

ctt aac tgg tgc agt gac atc ttt tac atg ttt gct ggg atc atc tct 371
Leu Asn Trp Cys Ser Asp Ile Phe Tyr Met Phe Ala Gly Ile Ile Ser
50 55 60

ctt ctc aac tac tta act tcc aga tcg cct gcc tgt gat gaa aac gtc 419

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Leu Leu Asn Tyr Leu Thr Ser Arg Ser Pro Ala Cys Asp Glu Asn Val
65                  70                  75                  80

act gtg att cca aca gag aga tca agg ctg ggg gtt ggt ccg gtg act      467
Thr Val Ile Pro Thr Glu Arg Ser Arg Leu Gly Val Gly Pro Val Thr
                85                  90                  95

aca gta tca cct gct aaa gat gaa ggg cca agg tct gag atg gaa tct      515
Thr Val Ser Pro Ala Lys Asp Glu Gly Pro Arg Ser Glu Met Glu Ser
            100                 105                 110

cta agt gtg aga gag aaa aat tta cca aag tca gga ctg tgg tgg          560
Leu Ser Val Arg Glu Lys Asn Leu Pro Lys Ser Gly Leu Trp Trp
        115                 120                 125

tgataggaaa acctaactat agcttgtctt aaaagcaggg gagaagctga gttgggaatg    620

gtcacataaa ttctgggaaa ctctcctaat atcatgtcca tattacttga ggagacagca    680

ttaaagctga tgaaatgtct tttgcgtgca ttggatccaa aatatatatg atagtcataa    740

agtaaataac tcacttaaga aaaacatttc taaaagaaaa caacaatgtt tagagtcatg    800

aatgaaagaa actagtgaaa gatgcagtgt gtagaccaga gacctctttg ggtatcaggg    860

atctcatgga ccagaatggc ccgtggagaa gaatgttaat tacttctgtt tggaattttc    920

tttattatgt gtggctttgg gtatactcag gatggaaagc acttggacaa atactgttga    980

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            20                  25                  30

Trp His Thr Arg Asp Ala Met Glu Ser Asp Leu Leu Trp Thr Tyr Tyr
        35                  40                  45

Leu Asn Trp Cys Ser Asp Ile Phe Tyr Met Phe Ala Gly Ile Ile Ser
    50                  55                  60

Leu Leu Asn Tyr Leu Thr Ser Arg Ser Pro Ala Cys Asp Glu Asn Val
65                  70                  75                  80

Thr Val Ile Pro Thr Glu Arg Ser Arg Leu Gly Val Gly Pro Val Thr
                85                  90                  95

Thr Val Ser Pro Ala Lys Asp Glu Gly Pro Arg Ser Glu Met Glu Ser
            100                 105                 110

Leu Ser Val Arg Glu Lys Asn Leu Pro Lys Ser Gly Leu Trp Trp
        115                 120                 125
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<210> 236
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<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (152)..(895)

)OCID: <WO_____.03089583A2 I_>

<223>

<400> 236

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gttggcattc ggtggtcctg gcagttagct gagcacgccc tctgagccgc tcggtggaca      60

ccaggcactc tagtaggcct ggcctaccca gaaacagcag gagagagaag aaacaggcca     120

gctgtgagaa gccaaggaca ccgagtcagt c atg gca cct aag gcg gca aag         172
                                  Met Ala Pro Lys Ala Ala Lys
                                  1               5

ggg gcc aag cca gag cca gca cca gct cca cct cca ccc ggg gcc aaa       220
Gly Ala Lys Pro Glu Pro Ala Pro Ala Pro Pro Pro Pro Gly Ala Lys
        10                  15                  20

ccc gag gaa gac aag aag gac ggt aag gag cca tcg gac aaa cct caa       268
Pro Glu Glu Asp Lys Lys Asp Gly Lys Glu Pro Ser Asp Lys Pro Gln
    25                  30                  35

aag gcg gtg cag gac cat aag gag cca tcg gac aaa cct caa aag gcg       316
Lys Ala Val Gln Asp His Lys Glu Pro Ser Asp Lys Pro Gln Lys Ala
40                  45                  50                  55

gtg cag ccc aag cac gaa gtg ggc acg agg agg ggg tgt cgc cgc tac       364
Val Gln Pro Lys His Glu Val Gly Thr Arg Arg Gly Cys Arg Arg Tyr
                60                  65                  70

cgg tgg gaa tta aaa gac agc aat aaa gag ttc tgg ctc ttg ggg cac       412
Arg Trp Glu Leu Lys Asp Ser Asn Lys Glu Phe Trp Leu Leu Gly His
            75                  80                  85

gct gag atc aag att cgg agt ttg ggc tgc cta ata gct gca atg ata       460
Ala Glu Ile Lys Ile Arg Ser Leu Gly Cys Leu Ile Ala Ala Met Ile
        90                  95                  100

ctg ttg tcc tca ctc acc gtg cac ccc atc ttg agg ctt atc atc acc       508
Leu Leu Ser Ser Leu Thr Val His Pro Ile Leu Arg Leu Ile Ile Thr
    105                 110                 115

atg gag ata tcc ttc ttc agc ttc ttc atc tta ctg tac agc ttt gcc       556
Met Glu Ile Ser Phe Phe Ser Phe Phe Ile Leu Leu Tyr Ser Phe Ala
120                 125                 130                 135

att cat aga tac ata ccc ttc atc ctg tgg ccc att tct gac ctc ttc       604
Ile His Arg Tyr Ile Pro Phe Ile Leu Trp Pro Ile Ser Asp Leu Phe
                140                 145                 150

aac gac ctg att gct tgt gcg ttc ctt gtg gga gcc gtg gtc ttt gct       652
Asn Asp Leu Ile Ala Cys Ala Phe Leu Val Gly Ala Val Val Phe Ala
            155                 160                 165

gtg aga agt cgg cga tcc atg aat ctc cac tac tta ctt gct gtg atc       700
Val Arg Ser Arg Arg Ser Met Asn Leu His Tyr Leu Leu Ala Val Ile
        170                 175                 180

ctt att ggt gcg gct gga gtt ttt gct ttt atc gat gtg tgt ctt caa       748
Leu Ile Gly Ala Ala Gly Val Phe Ala Phe Ile Asp Val Cys Leu Gln
    185                 190                 195

aga aac cac ttc aga ggc aag aag gcc aaa aag cat atg ctg gtt cct       796
-Arg Asn His Phe Arg Gly Lys Lys Ala Lys Lys His Met Leu Val Pro
200                 205                 210                 215

cct cca gga aag gaa aaa gga ccc cag cag ggc aag gga cca gaa ccc       844
Pro Pro Gly Lys Glu Lys Gly Pro Gln Gln Gly Lys Gly Pro Glu Pro
                220                 225                 230

gcc aag cca cca gaa cct ggc aag cca cca ggg cca gca aag gga aag       892
Ala Lys Pro Pro Glu Pro Gly Lys Pro Pro Gly Pro Ala Lys Gly Lys
            235                 240                 245

aaa tgacttggag gaggctcctg gtgtctgaaa cggcagtgta ttttacagca           945
Lys


atatgtttcc actctcttcc ttgtcttctt tctggaatgg ttttcttttc cattttcatt   1005

accacctttg cttggaaaag aatggattaa tggattctaa aagcctaaa               1054
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<210> 237
<211> 248
<212> PRT
<213> Homo sapiens

<400> 237

Met Ala Pro Lys Ala Ala Lys Gly Ala Lys Pro Glu Pro Ala Pro Ala
1 5 10 15

Pro Pro Pro Pro Gly Ala Lys Pro Glu Glu Asp Lys Lys Asp Gly Lys
20 25 30

Glu Pro Ser Asp Lys Pro Gln Lys Ala Val Gln Asp His Lys Glu Pro
35 40 45

Ser Asp Lys Pro Gln Lys Ala Val Gln Pro Lys His Glu Val Gly Thr
50 55 60

Arg Arg Gly Cys Arg Arg Tyr Arg Trp Glu Leu Lys Asp Ser Asn Lys
65 70 75 80

Glu Phe Trp Leu Leu Gly His Ala Glu Ile Lys Ile Arg Ser Leu Gly
85 90 95

Cys Leu Ile Ala Ala Met Ile Leu Leu Ser Ser Leu Thr Val His Pro
100 105 110

Ile Leu Arg Leu Ile Ile Thr Met Glu Ile Ser Phe Phe Ser Phe Phe
115 120 125

Ile Leu Leu Tyr Ser Phe Ala Ile His Arg Tyr Ile Pro Phe Ile Leu
130 135 140

Trp Pro Ile Ser Asp Leu Phe Asn Asp Leu Ile Ala Cys Ala Phe Leu
145 150 155 160

Val Gly Ala Val Val Phe Ala Val Arg Ser Arg Arg Ser Met Asn Leu
165 170 175

His Tyr Leu Leu Ala Val Ile Leu Ile Gly Ala Ala Gly Val Phe Ala
180 185 190

Phe Ile Asp Val Cys Leu Gln Arg Asn His Phe Arg Gly Lys Lys Ala
195 200 205

Lys Lys His Met Leu Val Pro Pro Pro Gly Lys Glu Lys Gly Pro Gln
210 215 220

Gln Gly Lys Gly Pro Glu Pro Ala Lys Pro Pro Glu Pro Gly Lys Pro
225 230 235 240

Pro Gly Pro Ala Lys Gly Lys Lys
245

<210> 238
<211> 487
<212> DNA
<213> Homo sapiens

<220>
<221> CDS

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<222> (17)..(418)
<223>

<400> 238
agtggcagct tggctg atg agc tat aag cca gcc ttg ttt ggg ttc cta ttc 52
Met Ser Tyr Lys Pro Ala Leu Phe Gly Phe Leu Phe
1 5 10

ctt ctg ctg ttg ctt agc aac tgg ttg gtc aag tat gaa cac aag ctc 100
Leu Leu Leu Leu Leu Ser Asn Trp Leu Val Lys Tyr Glu His Lys Leu
15 20 25

acc ctc cca gag ccc cag cag gag gaa gag aaa cca aag act tct gaa 148
Thr Leu Pro Glu Pro Gln Gln Glu Glu Glu Lys Pro Lys Thr Ser Glu
30 35 40

aac gac tcc aag aac agc aag gcc gtg aac aca aaa gaa gtc aat aga 196
Asn Asp Ser Lys Asn Ser Lys Ala Val Asn Thr Lys Glu Val Asn Arg
45 50 55 60

acg cat gcc tgc ttt gcc ctc cag gac gag atc ctc caa cgg ctg ttg 244
Thr His Ala Cys Phe Ala Leu Gln Asp Glu Ile Leu Gln Arg Leu Leu
65 70 75

ttc agt gaa atg aag atg aag gtc cta gaa aat cag atg ttc atc ata 292
Phe Ser Glu Met Lys Met Lys Val Leu Glu Asn Gln Met Phe Ile Ile
80 85 90

tgg aat aaa atg aat cac cac ggg cgg tca agc aga cat cgg aat ttt 340
Trp Asn Lys Met Asn His His Gly Arg Ser Ser Arg His Arg Asn Phe
95 100 105

ccc atg aaa aaa cac aga atg agg agg cat gag tca att tgc ccc acc 388
Pro Met Lys Lys His Arg Met Arg Arg His Glu Ser Ile Cys Pro Thr
110 115 120

ctg tct gac tgt act tcg agt tcc ccc agc taatgaggcc gaggcgggct 438
Leu Ser Asp Cys Thr Ser Ser Ser Pro Ser
125 130

ggcctctgcc gatgttacct tttacctcag taaaacccag tcacagcct 487

<210> 239
<211> 134
<212> PRT
<213> Homo sapiens

<400> 239

Met Ser Tyr Lys Pro Ala Leu Phe Gly Phe Leu Phe Leu Leu Leu Leu
1 5 10 15

Leu Ser Asn Trp Leu Val Lys Tyr Glu His Lys Leu Thr Leu Pro Glu
20 25 30

Pro Gln Gln Glu Glu Glu Lys Pro Lys Thr Ser Glu Asn Asp Ser Lys
35 40 45

Asn Ser Lys Ala Val Asn Thr Lys Glu Val Asn Arg Thr His Ala Cys
50 55 60

Phe Ala Leu Gln Asp Glu Ile Leu Gln Arg Leu Leu Phe Ser Glu Met
65 70 75 80

Lys Met Lys Val Leu Glu Asn Gln Met Phe Ile Ile Trp Asn Lys Met
85 90 95

Asn His His Gly Arg Ser Ser Arg His Arg Asn Phe Pro Met Lys Lys
100 105 110

His Arg Met Arg Arg His Glu Ser Ile Cys Pro Thr Leu Ser Asp Cys

OCID: <WO_____03089583A2_I_>

115 120 125

Thr Ser Ser Ser Pro Ser
130

<210> 240
<211> 846
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (108)..(725)
<223>

<400> 240
attctggaga ctctgattgg ctgggcagat gggctgactg gctgggcaga tgggtgggtg 60

agttccctct ccccagagcc atcggccagg taccaaagct cagctgt atg gat tcc 116
Met Asp Ser
1

caa cag gag gac ctg cgc ttc cct ggg atg tgg gtc tca ttg tac ttt 164
Gln Gln Glu Asp Leu Arg Phe Pro Gly Met Trp Val Ser Leu Tyr Phe
5 10 15

gga atc ctg ggg ctg tgt tct gtg ata act gga ggg tgc att atc ttt 212
Gly Ile Leu Gly Leu Cys Ser Val Ile Thr Gly Gly Cys Ile Ile Phe
20 25 30 35

ctg cac tgg agg aag aac ttg agg cgg gaa gag cat gcc cag cag tgg 260
Leu His Trp Arg Lys Asn Leu Arg Arg Glu Glu His Ala Gln Gln Trp
40 45 50

gtg gag gtg atg aga gct gcc aca ttc acc tac agc cca ttg ttg tac 308
Val Glu Val Met Arg Ala Ala Thr Phe Thr Tyr Ser Pro Leu Leu Tyr
55 60 65

tgg att aac aag cga cgg cgc tac ggc atg aat gca gcc atc aac acg 356
Trp Ile Asn Lys Arg Arg Arg Tyr Gly Met Asn Ala Ala Ile Asn Thr
70 75 80

ggc cct gcc cct gct gtc acc aag act gag act gag gtc cag aat cca 404
Gly Pro Ala Pro Ala Val Thr Lys Thr Glu Thr Glu Val Gln Asn Pro
85 90 95

gat gtt ctg tgg gat ttg gac atc ccc gaa ggc agg agc cat gct gac 452
Asp Val Leu Trp Asp Leu Asp Ile Pro Glu Gly Arg Ser His Ala Asp
100 105 110 115

caa gac agc aac ccc aag gcg gaa gcc cct gct ccc ctg caa cct gca 500
Gln Asp Ser Asn Pro Lys Ala Glu Ala Pro Ala Pro Leu Gln Pro Ala
120 125 130

ctg cag ctg gct cca cag cag ccc cag gcc aga tcc cca ttc cca ctt 548
Leu Gln Leu Ala Pro Gln Gln Pro Gln Ala Arg Ser Pro Phe Pro Leu
135 140 145

ccc atc ttt cag gag gtg ccc ttt gcc cca ccc ttg tgc aac cta ccc 596
Pro Ile Phe Gln Glu Val Pro Phe Ala Pro Pro Leu Cys Asn Leu Pro
150 155 160

ccc ctg ctg aac cac tct gtc tcc tat cct ttg gcc acc tgt cct gaa 644
Pro Leu Leu Asn His Ser Val Ser Tyr Pro Leu Ala Thr Cys Pro Glu
165 170 175

agg aat gtt ctc ttc cat tcc ctc ctg aat ctg gcc cag gaa gac cat 692
Arg Asn Val Leu Phe His Ser Leu Leu Asn Leu Ala Gln Glu Asp His
180 185 190 195

agc ttc aat gcc aag cct ttt cct tca gaa ctg tagcctcctc tcactgaagg 745
Ser Phe Asn Ala Lys Pro Phe Pro Ser Glu Leu
200 205

tgggagctgc aggaatcagg tgcagagtag gaaatggaac taacctcagg aaggtggtat 805

tgacagaggt caggacccac ctggatgtca tgctatgaaa c 846

DOCID: <WO 03089583A2 I >

<210> 241
<211> 206
<212> PRT
<213> Homo sapiens

<400> 241

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Met Asp Ser Gln Gln Glu Asp Leu Arg Phe Pro Gly Met Trp Val Ser
1               5                  10                  15

Leu Tyr Phe Gly Ile Leu Gly Leu Cys Ser Val Ile Thr Gly Gly Cys
            20                  25                  30

Ile Ile Phe Leu His Trp Arg Lys Asn Leu Arg Arg Glu Glu His Ala
        35                  40                  45

Gln Gln Trp Val Glu Val Met Arg Ala Ala Thr Phe Thr Tyr Ser Pro
    50                  55                  60

Leu Leu Tyr Trp Ile Asn Lys Arg Arg Arg Tyr Gly Met Asn Ala Ala
65                  70                  75                  80

Ile Asn Thr Gly Pro Ala Pro Ala Val Thr Lys Thr Glu Thr Glu Val
                85                  90                  95

Gln Asn Pro Asp Val Leu Trp Asp Leu Asp Ile Pro Glu Gly Arg Ser
            100                 105                 110

His Ala Asp Gln Asp Ser Asn Pro Lys Ala Glu Ala Pro Ala Pro Leu
        115                 120                 125

Gln Pro Ala Leu Gln Leu Ala Pro Gln Gln Pro Gln Ala Arg Ser Pro
    130                 135                 140

Phe Pro Leu Pro Ile Phe Gln Glu Val Pro Phe Ala Pro Pro Leu Cys
145                 150                 155                 160

Asn Leu Pro Pro Leu Leu Asn His Ser Val Ser Tyr Pro Leu Ala Thr
                165                 170                 175

Cys Pro Glu Arg Asn Val Leu Phe His Ser Leu Leu Asn Leu Ala Gln
            180                 185                 190

Glu Asp His Ser Phe Asn Ala Lys Pro Phe Pro Ser Glu Leu
        195                 200                 205
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<210> 242
<211> 663
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (40)..(585)
<223>

<400> 242

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tagttcctag agctgctgct tattaaaatg tcaacatct tca tct tct agc tgg        54
                                          Ser Ser Ser Ser Trp
                                          1               5

gac aac ctc tta gag tct ctc tct ctc agc aca gta tgg aat tgg ata       102
Asp Asn Leu Leu Glu Ser Leu Ser Leu Ser Thr Val Trp Asn Trp Ile
                10                  15                  20
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caa gca agt ttt ttg gga gag act agt gca cct cag caa aca agt ttg      150
Gln Ala Ser Phe Leu Gly Glu Thr Ser Ala Pro Gln Gln Thr Ser Leu
            25                  30                  35

gga cta tta gat aat ctt gct cca gct gtg caa atc atc ttg agg att      198
Gly Leu Leu Asp Asn Leu Ala Pro Ala Val Gln Ile Ile Leu Arg Ile
        40                  45                  50

tct ttc ttg att tta ttg gga ata gga ata tat gcc tta tgg aaa cga      246
Ser Phe Leu Ile Leu Leu Gly Ile Gly Ile Tyr Ala Leu Trp Lys Arg
    55                  60                  65

agt att cag tca att cag aaa aca ttg ttg ttt gta atc aca ctc tac      294
Ser Ile Gln Ser Ile Gln Lys Thr Leu Leu Phe Val Ile Thr Leu Tyr
70                  75                  80                  85

aaa ctt tac aag aag ggc tca cat att ttt gag gct ttg cta gcc aac      342
Lys Leu Tyr Lys Lys Gly Ser His Ile Phe Glu Ala Leu Leu Ala Asn
                90                  95                  100

cca gaa gga agt ggt ctc cga att caa gac aat aat aat ctt ttc ctg      390
Pro Glu Gly Ser Gly Leu Arg Ile Gln Asp Asn Asn Asn Leu Phe Leu
            105                 110                 115

tcc ttg ggt ctg caa gag aaa att ttg aaa aaa ctt aag aca gtg gaa      438
Ser Leu Gly Leu Gln Glu Lys Ile Leu Lys Lys Leu Lys Thr Val Glu
        120                 125                 130

aac aaa atg aag aac cta gaa ggg ata atc gtt gct caa aaa cct gcc      486
Asn Lys Met Lys Asn Leu Glu Gly Ile Ile Val Ala Gln Lys Pro Ala
    135                 140                 145

acg aag agg gat tgc tcc tct gag ccc tac tgc agc tgc tct gac tgc      534
Thr Lys Arg Asp Cys Ser Ser Glu Pro Tyr Cys Ser Cys Ser Asp Cys
150                 155                 160                 165

cag agt ccc ttg tcc aca tca ggg ttt act tcc ccc att tga aat gtg      582
Gln Ser Pro Leu Ser Thr Ser Gly Phe Thr Ser Pro Ile     Asn Val
                170                 175                 180

atg gactccaatc ttttccagga aagcactgtt tccctcatgt gtgcagtggt           635
Met

gtatcaataa agatagagaa cgctattg                                      663
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<210> 243
<211> 178
<212> PRT
<213> Homo sapiens

<400> 243

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Ser Ser Ser Ser Trp Asp Asn Leu Leu Glu Ser Leu Ser Leu Ser Thr
1               5                   10                  15

Val Trp Asn Trp Ile Gln Ala Ser Phe Leu Gly Glu Thr Ser Ala Pro
            20                  25                  30

Gln Gln Thr Ser Leu Gly Leu Leu Asp Asn Leu Ala Pro Ala Val Gln
        35                  40                  45

Ile Ile Leu Arg Ile Ser Phe Leu Ile Leu Leu Gly Ile Gly Ile Tyr
    50                  55                  60

Ala Leu Trp Lys Arg Ser Ile Gln Ser Ile Gln Lys Thr Leu Leu Phe
65                  70                  75                  80

Val Ile Thr Leu Tyr Lys Leu Tyr Lys Lys Gly Ser His Ile Phe Glu
                85                  90                  95
```


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Ala Leu Leu Ala Asn Pro Glu Gly Ser Gly Leu Arg Ile Gln Asp Asn
100 105 110

Asn Asn Leu Phe Leu Ser Leu Gly Leu Gln Glu Lys Ile Leu Lys Lys
115 120 125

Leu Lys Thr Val Glu Asn Lys Met Lys Asn Leu Glu Gly Ile Ile Val
130 135 140

Ala Gln Lys Pro Ala Thr Lys Arg Asp Cys Ser Ser Glu Pro Tyr Cys
145 150 155 160

Ser Cys Ser Asp Cys Gln Ser Pro Leu Ser Thr Ser Gly Phe Thr Ser
165 170 175

Pro Ile

<210> 244
<211> 541
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (62)..(349)
<223>

<400> 244
catatctgtt gccactctga gtttggcatt atgtgttcga attttaacca catatctatt 60

g atg tgc ttt gct ggt ttt agt ttt aag gag aaa ata ttt att gct tta 109
Met Cys Phe Ala Gly Phe Ser Phe Lys Glu Lys Ile Phe Ile Ala Leu
1 5 10 15

gca tgg atg ccc aaa gct aca gta cag gct gtg tta ggt cct ctg gct 157
Ala Trp Met Pro Lys Ala Thr Val Gln Ala Val Leu Gly Pro Leu Ala
20 25 30

cta gaa aca gca aga gtc tct gca ccc cac ttg gaa cca tat gcg aag 205
Leu Glu Thr Ala Arg Val Ser Ala Pro His Leu Glu Pro Tyr Ala Lys
35 40 45

gat gtg atg tca gta gca ttt tta gcc atc tcg atc aca gct cca aat 253
Asp Val Met Ser Val Ala Phe Leu Ala Ile Ser Ile Thr Ala Pro Asn
50 55 60

gga gct cta ctt atg ggc att ctg ggg cct aaa atg ctt aca cgc cat 301
Gly Ala Leu Leu Met Gly Ile Leu Gly Pro Lys Met Leu Thr Arg His
65 70 75 80

tat gat cca agc aaa ata aaa ctg caa ttg tca aca tta gaa cat cat 349
Tyr Asp Pro Ser Lys Ile Lys Leu Gln Leu Ser Thr Leu Glu His His
85 90 95

taaaaagttt acctgtcatc atctgcctgc ttctttttaat gaattatttc acatgacaga 409

agaattttaa agtagaaata tgtagggact gtacagaaaa tccaggattt agtaaacatg 469

tgatttcagt acagggcttt tcttggactt tttactccaa agttaattta ataaaaataa 529

tattaaatgg aa 541

<210> 245
<211> 96
<212> PRT
<213> Homo sapiens

<400> 245

Met Cys Phe Ala Gly Phe Ser Phe Lys Glu Lys Ile Phe Ile Ala Leu
1 5 10 15

OCID: <WO_____03089583A2.I_>

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Ala Trp Met Pro Lys Ala Thr Val Gln Ala Val Leu Gly Pro Leu Ala
            20                  25                  30

Leu Glu Thr Ala Arg Val Ser Ala Pro His Leu Glu Pro Tyr Ala Lys
        35                  40                  45

Asp Val Met Ser Val Ala Phe Leu Ala Ile Ser Ile Thr Ala Pro Asn
    50                  55                  60

Gly Ala Leu Leu Met Gly Ile Leu Gly Pro Lys Met Leu Thr Arg His
65                  70                  75                  80

Tyr Asp Pro Ser Lys Ile Lys Leu Gln Leu Ser Thr Leu Glu His His
                85                  90                  95
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<210> 246
<211> 2499
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (128)..(2284)
<223>

<400> 246

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gcaagaggcc ccttgtggcc accgagtcct ccgacgccct cgccaggctg gcctttgggt     60

tggcccaggc aggacgggct gccgagagca ctcgggccgc gtcgccagga gccgcccagg    120

gtgagcc atg ttc gta ggc gtc gcc cgg cac tct ggg agc cag gat gaa       169
        Met Phe Val Gly Val Ala Arg His Ser Gly Ser Gln Asp Glu
        1               5                   10

gtc tca agg gga gta gag ccg ctg gag gcc gcg cgg gcc cag cct gct      217
Val Ser Arg Gly Val Glu Pro Leu Glu Ala Ala Arg Ala Gln Pro Ala
15                  20                  25                  30

aag gac agg agg gcc aag gga acc ccg aag tcc tcg aag ccc ggg aaa      265
Lys Asp Arg Arg Ala Lys Gly Thr Pro Lys Ser Ser Lys Pro Gly Lys
                35                  40                  45

aaa cac cgg tat ctg aga cta ctt cca gag gcc ttg ata agg ttc ggc      313
Lys His Arg Tyr Leu Arg Leu Leu Pro Glu Ala Leu Ile Arg Phe Gly
            50                  55                  60

ggt ttc cga aaa agg aaa aaa gcc aag tcc tca gtt tcc aag aag ccg      361
Gly Phe Arg Lys Arg Lys Lys Ala Lys Ser Ser Val Ser Lys Lys Pro
        65                  70                  75

gga gaa gtg gat gac agt ttg gag cag ccc tgt ggt ttg ggc tgc tta      409
Gly Glu Val Asp Asp Ser Leu Glu Gln Pro Cys Gly Leu Gly Cys Leu
    80                  85                  90

gtc agc acc tgc tgt gag tgt tgc aat aac att cgc tgc ttc atg att      457
Val Ser Thr Cys Cys Glu Cys Cys Asn Asn Ile Arg Cys Phe Met Ile
95                  100                 105                 110

ttc tac tgc atc ctg ctc ata tgt caa ggt gtg gtg ttt ggt ctt ata      505
Phe Tyr Cys Ile Leu Leu Ile Cys Gln Gly Val Val Phe Gly Leu Ile
                115                 120                 125

gat gtc agc att ggc gat ttt cag aag gaa tat caa ctg aaa acc att      553
Asp Val Ser Ile Gly Asp Phe Gln Lys Glu Tyr Gln Leu Lys Thr Ile
            130                 135                 140

gag aag ttg gca ttg gaa aag agt tac gat att tca tct ggc ctg gta      601
Glu Lys Leu Ala Leu Glu Lys Ser Tyr Asp Ile Ser Ser Gly Leu Val
        145                 150                 155

gca ata ttt ata gca ttc tat gga gac aga aaa aaa gta ata tgg ttt      649
Ala Ile Phe Ile Ala Phe Tyr Gly Asp Arg Lys Lys Val Ile Trp Phe
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    160                 165                 170

gta gct tcc tcc ttt tta ata gga ctt gga tca ctt tta tgt gct ttt      697
Val Ala Ser Ser Phe Leu Ile Gly Leu Gly Ser Leu Leu Cys Ala Phe
175                 180                 185                 190

cca tcc att aat gaa gaa aat aaa caa agt aag gta gga att gaa gat      745
Pro Ser Ile Asn Glu Glu Asn Lys Gln Ser Lys Val Gly Ile Glu Asp
                195                 200                 205

att tgc gaa gaa ata aag gtt gtc agt ggt tgc cag agc agt ggt ata      793
Ile Cys Glu Glu Ile Lys Val Val Ser Gly Cys Gln Ser Ser Gly Ile
            210                 215                 220

tca ttc caa tca aaa tac ctg tct ttc ttc atc ctt ggg cag act gtg      841
Ser Phe Gln Ser Lys Tyr Leu Ser Phe Phe Ile Leu Gly Gln Thr Val
        225                 230                 235

cag gga ata gca gga atg cct ctt tat atc ctt gga ata acc ttt att      889
Gln Gly Ile Ala Gly Met Pro Leu Tyr Ile Leu Gly Ile Thr Phe Ile
    240                 245                 250

gat gag aat gtt gct aca cac tca gct ggt atc tat tta ggt att gca      937
Asp Glu Asn Val Ala Thr His Ser Ala Gly Ile Tyr Leu Gly Ile Ala
255                 260                 265                 270

gaa tgt aca tca atg att gga tat gct ctg ggt tat gtg cta gga gca      985
Glu Cys Thr Ser Met Ile Gly Tyr Ala Leu Gly Tyr Val Leu Gly Ala
                275                 280                 285

cca cta gtt aaa gtc cct gag aat act act tct gca aca aac act aca     1033
Pro Leu Val Lys Val Pro Glu Asn Thr Thr Ser Ala Thr Asn Thr Thr
            290                 295                 300

gtc aat aat ggt agt cca gaa tgg cta tgg act tgg tgg att aat ttt     1081
Val Asn Asn Gly Ser Pro Glu Trp Leu Trp Thr Trp Trp Ile Asn Phe
        305                 310                 315

ctt ttt gcc gct gtc gtt gca tgg tgt aca tta ata cca ttg tca tgc     1129
Leu Phe Ala Ala Val Val Ala Trp Cys Thr Leu Ile Pro Leu Ser Cys
    320                 325                 330

ttt cca aac aat atg cca ggt tca aca cgg ata aaa gct agg aaa cgt     1177
Phe Pro Asn Asn Met Pro Gly Ser Thr Arg Ile Lys Ala Arg Lys Arg
335                 340                 345                 350

aaa cag ctt cat ttt ttt gac agc aga ctt aaa gat ctg aaa ctt gga     1225
Lys Gln Leu His Phe Phe Asp Ser Arg Leu Lys Asp Leu Lys Leu Gly
                355                 360                 365

act aat atc aag gat tta tgt gct gct ctt tgg att ctg atg agg aat     1273
Thr Asn Ile Lys Asp Leu Cys Ala Ala Leu Trp Ile Leu Met Arg Asn
            370                 375                 380

cca gtg ctc ata tgc cta gct ctg tca aaa gct aca gaa tat tta gtt     1321
Pro Val Leu Ile Cys Leu Ala Leu Ser Lys Ala Thr Glu Tyr Leu Val
        385                 390                 395

att att gga gct tct gaa ttt ttg cct ata tat tta gaa aat cag ttt     1369
Ile Ile Gly Ala Ser Glu Phe Leu Pro Ile Tyr Leu Glu Asn Gln Phe
    400                 405                 410

ata tta aca ccc act gtg gca act aca ctt gca gga ctt gtt tta att     1417
Ile Leu Thr Pro Thr Val Ala Thr Thr Leu Ala Gly Leu Val Leu Ile
415                 420                 425                 430

cca gga ggt gca ctt ggc cag ctt ctg gga ggt gtc att gtt tcc aca     1465
Pro Gly Gly Ala Leu Gly Gln Leu Leu Gly Gly Val Ile Val Ser Thr
                435                 440                 445

tta gaa atg tct tgt aaa gcc ctt atg aga ttt ata atg gtt aca tct     1513
Leu Glu Met Ser Cys Lys Ala Leu Met Arg Phe Ile Met Val Thr Ser
            450                 455                 460

gtg ata tca ctt ata ctg ctt gtg ttt att att ttt gta cgc tgt aat     1561
Val Ile Ser Leu Ile Leu Leu Val Phe Ile Ile Phe Val Arg Cys Asn
        465                 470                 475

cca gtg caa ttt gct ggg atc aat gaa gat tat gat gga aca agg aag     1609
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Pro Val Gln Phe Ala Gly Ile Asn Glu Asp Tyr Asp Gly Thr Arg Lys
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ttg gga aac ctc acg gct cct tgc aat gaa aaa tgt aga tgc tca tct     1657
Leu Gly Asn Leu Thr Ala Pro Cys Asn Glu Lys Cys Arg Cys Ser Ser
495                 500                 505                 510

tca att tat tct tct ata tgt gga aga gat gat att gaa tat ttt tct     1705
Ser Ile Tyr Ser Ser Ile Cys Gly Arg Asp Asp Ile Glu Tyr Phe Ser
                515                 520                 525

gcc tgc ttt gca ggg tgt aca tat tct aaa gca caa aac caa aaa aag     1753
Ala Cys Phe Ala Gly Cys Thr Tyr Ser Lys Ala Gln Asn Gln Lys Lys
            530                 535                 540

atg tac tac aat tgt tct tgc att aaa gaa gga tta ata act gca gat     1801
Met Tyr Tyr Asn Cys Ser Cys Ile Lys Glu Gly Leu Ile Thr Ala Asp
        545                 550                 555

gca gaa ggt gat ttt att gat gcc aga ccc ggg aaa tgt gat gca aag     1849
Ala Glu Gly Asp Phe Ile Asp Ala Arg Pro Gly Lys Cys Asp Ala Lys
    560                 565                 570

tgc tat aag tta cct ttg ttc att gct ttt atc ttt tct aca ctt ata     1897
Cys Tyr Lys Leu Pro Leu Phe Ile Ala Phe Ile Phe Ser Thr Leu Ile
575                 580                 585                 590

ttt tct ggt ttt tct ggt gta cca atc gtc ttg gcc atg acg cgg gtt     1945
Phe Ser Gly Phe Ser Gly Val Pro Ile Val Leu Ala Met Thr Arg Val
                595                 600                 605

gta cct gac aaa ctg cgt tct ctg gcc ttg ggt gta agc tat gtg att     1993
Val Pro Asp Lys Leu Arg Ser Leu Ala Leu Gly Val Ser Tyr Val Ile
            610                 615                 620

ttg aga ata ttt ggg act att cct gga cca tca atc ttt aaa atg tca     2041
Leu Arg Ile Phe Gly Thr Ile Pro Gly Pro Ser Ile Phe Lys Met Ser
        625                 630                 635

gga gaa act tct tgt att tta cgg gat gtt aat aaa tgt gga cac aca     2089
Gly Glu Thr Ser Cys Ile Leu Arg Asp Val Asn Lys Cys Gly His Thr
    640                 645                 650

gga cgt tgt tgg ata tat aac aag aca aaa atg gct ttc tta ttg gta     2137
Gly Arg Cys Trp Ile Tyr Asn Lys Thr Lys Met Ala Phe Leu Leu Val
655                 660                 665                 670

gga ata tgt ttt ctt tgc aaa cta tgc act atc atc ttc act act att     2185
Gly Ile Cys Phe Leu Cys Lys Leu Cys Thr Ile Ile Phe Thr Thr Ile
                675                 680                 685

gca ttt ttc ata tac aaa cgt cgt cta aat gag aac act gac ttc cca     2233
Ala Phe Phe Ile Tyr Lys Arg Arg Leu Asn Glu Asn Thr Asp Phe Pro
            690                 695                 700

gat gta act gtg aag aat cca aaa gtt aag aaa aaa gaa gaa act gac     2281
Asp Val Thr Val Lys Asn Pro Lys Val Lys Lys Lys Glu Glu Thr Asp
        705                 710                 715

ttg taactggatc atcattgtga ttgcagatca tttgaggatc agagtgtgaa          2334
Leu

aacgagtttc tcttttacag attctccaag atttgtttct gtgcccaact ttcagaagag   2394

gaaaatcaca cattatgttt acataagtag caaaaatata tttatggtga tctgcatttt   2454

cataataaag tgtcctattg tgaaacaaaa aaaaaaaaaa aaaaa                   2499


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<213>  Homo sapiens

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20 25 30

Arg Arg Ala Lys Gly Thr Pro Lys Ser Ser Lys Pro Gly Lys Lys His
35 40 45

Arg Tyr Leu Arg Leu Leu Pro Glu Ala Leu Ile Arg Phe Gly Gly Phe
50 55 60

Arg Lys Arg Lys Lys Ala Lys Ser Ser Val Ser Lys Lys Pro Gly Glu
65 70 75 80

Val Asp Asp Ser Leu Glu Gln Pro Cys Gly Leu Gly Cys Leu Val Ser
85 90 95

Thr Cys Cys Glu Cys Cys Asn Asn Ile Arg Cys Phe Met Ile Phe Tyr
100 105 110

Cys Ile Leu Leu Ile Cys Gln Gly Val Val Phe Gly Leu Ile Asp Val
115 120 125

Ser Ile Gly Asp Phe Gln Lys Glu Tyr Gln Leu Lys Thr Ile Glu Lys
130 135 140

Leu Ala Leu Glu Lys Ser Tyr Asp Ile Ser Ser Gly Leu Val Ala Ile
145 150 155 160

Phe Ile Ala Phe Tyr Gly Asp Arg Lys Lys Val Ile Trp Phe Val Ala
165 170 175

Ser Ser Phe Leu Ile Gly Leu Gly Ser Leu Leu Cys Ala Phe Pro Ser
180 185 190

Ile Asn Glu Glu Asn Lys Gln Ser Lys Val Gly Ile Glu Asp Ile Cys
195 200 205

Glu Glu Ile Lys Val Val Ser Gly Cys Gln Ser Ser Gly Ile Ser Phe
210 215 220

Gln Ser Lys Tyr Leu Ser Phe Phe Ile Leu Gly Gln Thr Val Gln Gly
225 230 235 240

Ile Ala Gly Met Pro Leu Tyr Ile Leu Gly Ile Thr Phe Ile Asp Glu
245 250 255

Asn Val Ala Thr His Ser Ala Gly Ile Tyr Leu Gly Ile Ala Glu Cys
260 265 270

Thr Ser Met Ile Gly Tyr Ala Leu Gly Tyr Val Leu Gly Ala Pro Leu
275 280 285

Val Lys Val Pro Glu Asn Thr Thr Ser Ala Thr Asn Thr Thr Val Asn
290 295 300

Asn Gly Ser Pro Glu Trp Leu Trp Thr Trp Trp Ile Asn Phe Leu Phe
305 310 315 320

Ala Ala Val Val Ala Trp Cys Thr Leu Ile Pro Leu Ser Cys Phe Pro

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325 330 335

Asn Asn Met Pro Gly Ser Thr Arg Ile Lys Ala Arg Lys Arg Lys Gln
340 345 350

Leu His Phe Phe Asp Ser Arg Leu Lys Asp Leu Lys Leu Gly Thr Asn
355 360 365

Ile Lys Asp Leu Cys Ala Ala Leu Trp Ile Leu Met Arg Asn Pro Val
370 375 380

Leu Ile Cys Leu Ala Leu Ser Lys Ala Thr Glu Tyr Leu Val Ile Ile
385 390 395 400

Gly Ala Ser Glu Phe Leu Pro Ile Tyr Leu Glu Asn Gln Phe Ile Leu
405 410 415

Thr Pro Thr Val Ala Thr Thr Leu Ala Gly Leu Val Leu Ile Pro Gly
420 425 430

Gly Ala Leu Gly Gln Leu Leu Gly Gly Val Ile Val Ser Thr Leu Glu
435 440 445

Met Ser Cys Lys Ala Leu Met Arg Phe Ile Met Val Thr Ser Val Ile
450 455 460

Ser Leu Ile Leu Leu Val Phe Ile Ile Phe Val Arg Cys Asn Pro Val
465 470 475 480

Gln Phe Ala Gly Ile Asn Glu Asp Tyr Asp Gly Thr Arg Lys Leu Gly
485 490 495

Asn Leu Thr Ala Pro Cys Asn Glu Lys Cys Arg Cys Ser Ser Ser Ile
500 505 510

Tyr Ser Ser Ile Cys Gly Arg Asp Asp Ile Glu Tyr Phe Ser Ala Cys
515 520 525

Phe Ala Gly Cys Thr Tyr Ser Lys Ala Gln Asn Gln Lys Lys Met Tyr
530 535 540

Tyr Asn Cys Ser Cys Ile Lys Glu Gly Leu Ile Thr Ala Asp Ala Glu
545 550 555 560

Gly Asp Phe Ile Asp Ala Arg Pro Gly Lys Cys Asp Ala Lys Cys Tyr
565 570 575

Lys Leu Pro Leu Phe Ile Ala Phe Ile Phe Ser Thr Leu Ile Phe Ser
580 585 590

Gly Phe Ser Gly Val Pro Ile Val Leu Ala Met Thr Arg Val Val Pro
595 600 605

Asp Lys Leu Arg Ser Leu Ala Leu Gly Val Ser Tyr Val Ile Leu Arg
610 615 620

Ile Phe Gly Thr Ile Pro Gly Pro Ser Ile Phe Lys Met Ser Gly Glu
625 630 635 640

Thr Ser Cys Ile Leu Arg Asp Val Asn Lys Cys Gly His Thr Gly Arg
645 650 655

Cys Trp Ile Tyr Asn Lys Thr Lys Met Ala Phe Leu Leu Val Gly Ile
660 665 670

Cys Phe Leu Cys Lys Leu Cys Thr Ile Ile Phe Thr Thr Ile Ala Phe
675 680 685

Phe Ile Tyr Lys Arg Arg Leu Asn Glu Asn Thr Asp Phe Pro Asp Val
690 695 700

Thr Val Lys Asn Pro Lys Val Lys Lys Lys Glu Glu Thr Asp Leu
705 710 715

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Met Glu Ala Leu Pro Pro
1 5

gtc aga tcc agc ctt ttg ggg atc ctg ttg cag gtt acg agg ctc tca 102
Val Arg Ser Ser Leu Leu Gly Ile Leu Leu Gln Val Thr Arg Leu Ser
10 15 20

gtg ctg ttg gtt cag aac cga gat cac ctc tat aat ttc ctg ctc ctc 150
Val Leu Leu Val Gln Asn Arg Asp His Leu Tyr Asn Phe Leu Leu Leu
25 30 35

aag atc aac ctc ttc aac cac tgg gtg tca ggg ctg gcc cag gag gcc 198
Lys Ile Asn Leu Phe Asn His Trp Val Ser Gly Leu Ala Gln Glu Ala
40 45 50

cgg ggg tcc tgt aac tgg cag gcc cac cta ccc ctg gga gct gca gcc 246
Arg Gly Ser Cys Asn Trp Gln Ala His Leu Pro Leu Gly Ala Ala Ala
55 60 65 70

tgc ccc ctg ggc cag gct ctc tgg gct ggg ctg gct ctg ata cag gtc 294
Cys Pro Leu Gly Gln Ala Leu Trp Ala Gly Leu Ala Leu Ile Gln Val
75 80 85

ccc gta tgg ctg gtg cta cag gga ccc agg ctg atg tgg gct ggc atg 342
Pro Val Trp Leu Val Leu Gln Gly Pro Arg Leu Met Trp Ala Gly Met
90 95 100

tgg ggc agc acc aag ggc ctg ggc ctg gcc ttg ctc agt gcc tgg gag 390
Trp Gly Ser Thr Lys Gly Leu Gly Leu Ala Leu Leu Ser Ala Trp Glu
105 110 115

cag ctg ggc ctg tct gtg gcc atc tgg aca gat ctg ttt ttg tca tgt 438
Gln Leu Gly Leu Ser Val Ala Ile Trp Thr Asp Leu Phe Leu Ser Cys
120 125 130

ctg cac ggc ctg atg ttg gtg gcc ttg ctc ttg gtg gta gtg acc tgg 486
Leu His Gly Leu Met Leu Val Ala Leu Leu Leu Val Val Val Thr Trp
135 140 145 150

agg gtg tgt cag aag tcc cac tgc ttc cga ctg ggc agg cag ctc agt 534
Arg Val Cys Gln Lys Ser His Cys Phe Arg Leu Gly Arg Gln Leu Ser
155 160 165

aag gcc ttg caa gtg aac tgc gtg gta agg aag ctc ctg gta cag ctg 582
Lys Ala Leu Gln Val Asn Cys Val Val Arg Lys Leu Leu Val Gln Leu
170 175 180

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aga cgt ctg tat tgg tgg gtg gag act atg act gcc ctc acc tcc tgg 630
Arg Arg Leu Tyr Trp Trp Val Glu Thr Met Thr Ala Leu Thr Ser Trp
185 190 195

cac ctg gcc tat ctc atc acc tgg acc acc tgc ctg gcc tcc cac ctg 678
His Leu Ala Tyr Leu Ile Thr Trp Thr Thr Cys Leu Ala Ser His Leu
200 205 210

ctg cag gct gcc ttt gag cac acg acc cag ctg gcc gag gcc cag gag 726
Leu Gln Ala Ala Phe Glu His Thr Thr Gln Leu Ala Glu Ala Gln Glu
215 220 225 230

gtt gaa ccc cag gag gtc tca ggg tct tcc ttg ctg ccc tca ctg tct 774
Val Glu Pro Gln Glu Val Ser Gly Ser Ser Leu Leu Pro Ser Leu Ser
235 240 245

gcg tcc tcg gac tca gag tct gga aca gtt ttg cca gag caa gaa act 822
Ala Ser Ser Asp Ser Glu Ser Gly Thr Val Leu Pro Glu Gln Glu Thr
250 255 260

ccc aga gaa taaatgtatc cccatctgcc 851
Pro Arg Glu
265

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<213> Homo sapiens

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Met Glu Ala Leu Pro Pro Val Arg Ser Ser Leu Leu Gly Ile Leu Leu
1 5 10 15

Gln Val Thr Arg Leu Ser Val Leu Leu Val Gln Asn Arg Asp His Leu
20 25 30

Tyr Asn Phe Leu Leu Leu Lys Ile Asn Leu Phe Asn His Trp Val Ser
35 40 45

Gly Leu Ala Gln Glu Ala Arg Gly Ser Cys Asn Trp Gln Ala His Leu
50 55 60

Pro Leu Gly Ala Ala Ala Cys Pro Leu Gly Gln Ala Leu Trp Ala Gly
65 70 75 80

Leu Ala Leu Ile Gln Val Pro Val Trp Leu Val Leu Gln Gly Pro Arg
85 90 95

Leu Met Trp Ala Gly Met Trp Gly Ser Thr Lys Gly Leu Gly Leu Ala
100 105 110

Leu Leu Ser Ala Trp Glu Gln Leu Gly Leu Ser Val Ala Ile Trp Thr
115 120 125

Asp Leu Phe Leu Ser Cys Leu His Gly Leu Met Leu Val Ala Leu Leu
130 135 140

Leu Val Val Val Thr Trp Arg Val Cys Gln Lys Ser His Cys Phe Arg
145 150 155 160

Leu Gly Arg Gln Leu Ser Lys Ala Leu Gln Val Asn Cys Val Val Arg
165 170 175

Lys Leu Leu Val Gln Leu Arg Arg Leu Tyr Trp Trp Val Glu Thr Met
180 185 190

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Thr Ala Leu Thr Ser Trp His Leu Ala Tyr Leu Ile Thr Trp Thr Thr
        195                 200                 205

Cys Leu Ala Ser His Leu Leu Gln Ala Ala Phe Glu His Thr Thr Gln
    210                 215                 220

Leu Ala Glu Ala Gln Glu Val Glu Pro Gln Glu Val Ser Gly Ser Ser
225                 230                 235                 240

Leu Leu Pro Ser Leu Ser Ala Ser Ser Asp Ser Glu Ser Gly Thr Val
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Leu Pro Glu Gln Glu Thr Pro Arg Glu
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aaagttcaga cccaggaaaa tttccatagt acctta atg aaa aag ata gaa atc        114
                                        Met Lys Lys Ile Glu Ile
                                        1               5

agt ggg acg tgt ctt tcc ttt cat ctc ctt ttc ggc ttg gaa atc aga        162
Ser Gly Thr Cys Leu Ser Phe His Leu Leu Phe Gly Leu Glu Ile Arg
            10                  15                  20

atg aga agg att gtt ttt gct ggt gtt atc tta ttc cgc ctc tta ggt        210
Met Arg Arg Ile Val Phe Ala Gly Val Ile Leu Phe Arg Leu Leu Gly
        25                  30                  35

gtt atc tta ttc cgc ctc tta ggt gtt atc tta ttc ggc cgc tta ggt        258
Val Ile Leu Phe Arg Leu Leu Gly Val Ile Leu Phe Gly Arg Leu Gly
    40                  45                  50

gac ctg gga acc tgc cag aca aaa cct ggt cag tac tgg aaa gaa gag        306
Asp Leu Gly Thr Cys Gln Thr Lys Pro Gly Gln Tyr Trp Lys Glu Glu
55                  60                  65                  70

gtc cac att caa gat gtt gga ggt ttg att tgc aga gca tgc aat ctt        354
Val His Ile Gln Asp Val Gly Gly Leu Ile Cys Arg Ala Cys Asn Leu
                75                  80                  85

tca ctg ccc ttc cat gga tgt ctt tta gac ctg gga acc tgc cag gca        402
Ser Leu Pro Phe His Gly Cys Leu Leu Asp Leu Gly Thr Cys Gln Ala
            90                  95                  100

gaa cct ggt cag tac tgt aaa gaa gag gtc cac att caa ggt ggc att        450
Glu Pro Gly Gln Tyr Cys Lys Glu Glu Val His Ile Gln Gly Gly Ile
        105                 110                 115

caa tgg tat tca gtc aaa ggc tgc aca aag aac aca tca gag tgc ttc        498
Gln Trp Tyr Ser Val Lys Gly Cys Thr Lys Asn Thr Ser Glu Cys Phe
    120                 125                 130

aag agt act ctc gtc aag aga att ctg caa ctg cat gaa ctt gta act        546
Lys Ser Thr Leu Val Lys Arg Ile Leu Gln Leu His Glu Leu Val Thr
135                 140                 145                 150

act cac tgc tgc aat cat tct ttg tgc aat ttc tgagtcagtg gcccatatct      599
Thr His Cys Cys Asn His Ser Leu Cys Asn Phe
                155                 160

aaaatgcttg gcagatcaat cagtctcgaa gcctgacctg gctatcacaa aatgatggct      659
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attgtcaatt agcccacttc agaaacctca gacccttgta ggtagaagga attttgatct 719

gaaattgact ttggttttca atattcccaa tatctccccc accacctcca actcatctga 779

gaaat 784

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<212> PRT
<213> Homo sapiens

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Met Lys Lys Ile Glu Ile Ser Gly Thr Cys Leu Ser Phe His Leu Leu
1 5 10 15

Phe Gly Leu Glu Ile Arg Met Arg Arg Ile Val Phe Ala Gly Val Ile
20 25 30

Leu Phe Arg Leu Leu Gly Val Ile Leu Phe Arg Leu Leu Gly Val Ile
35 40 45

Leu Phe Gly Arg Leu Gly Asp Leu Gly Thr Cys Gln Thr Lys Pro Gly
50 55 60

Gln Tyr Trp Lys Glu Glu Val His Ile Gln Asp Val Gly Gly Leu Ile
65 70 75 80

Cys Arg Ala Cys Asn Leu Ser Leu Pro Phe His Gly Cys Leu Leu Asp
85 90 95

Leu Gly Thr Cys Gln Ala Glu Pro Gly Gln Tyr Cys Lys Glu Glu Val
100 105 110

His Ile Gln Gly Gly Ile Gln Trp Tyr Ser Val Lys Gly Cys Thr Lys
115 120 125

Asn Thr Ser Glu Cys Phe Lys Ser Thr Leu Val Lys Arg Ile Leu Gln
130 135 140

Leu His Glu Leu Val Thr Thr His Cys Cys Asn His Ser Leu Cys Asn
145 150 155 160

Phe

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<212> DNA
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<222> (24)..(1850)
<223>

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Met Ala Glu Ala Ser Arg Trp His Arg Gly
1 5 10

ggg gct tcg aaa cat aag ttg cat tac aga aag gaa gta gaa att aca 101
Gly Ala Ser Lys His Lys Leu His Tyr Arg Lys Glu Val Glu Ile Thr
15 20 25

acc aca ctt cag gaa ttg tta ctc tac ttt att ttt tta ata aac cta 149

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Thr Thr Leu Gln Glu Leu Leu Leu Tyr Phe Ile Phe Leu Ile Asn Leu
            30                  35                  40

tgt ata ttg act ttt ggg atg gta aac cca cat atg tat tac tta aac      197
Cys Ile Leu Thr Phe Gly Met Val Asn Pro His Met Tyr Tyr Leu Asn
        45                  50                  55

aag gtt atg tca tct cta ttt ttg gac act tct gtg cct ggt gaa gaa      245
Lys Val Met Ser Ser Leu Phe Leu Asp Thr Ser Val Pro Gly Glu Glu
    60                  65                  70

aga acc aac ttt aag tcc att cgc agc ata act gat ttt tgg aag ttt      293
Arg Thr Asn Phe Lys Ser Ile Arg Ser Ile Thr Asp Phe Trp Lys Phe
75                  80                  85                  90

atg gaa gga ccc ctt ttg gaa ggt ctg tac tgg gat tca tgg tac aat      341
Met Glu Gly Pro Leu Leu Glu Gly Leu Tyr Trp Asp Ser Trp Tyr Asn
                95                  100                 105

aac cag cag ctg tat aat tta aag aac agc agt cgc atc tac tat gaa      389
Asn Gln Gln Leu Tyr Asn Leu Lys Asn Ser Ser Arg Ile Tyr Tyr Glu
            110                 115                 120

aat ata ctt cta gga gtt ccc aga gtt cgt caa cta aaa gtc cgc aac      437
Asn Ile Leu Leu Gly Val Pro Arg Val Arg Gln Leu Lys Val Arg Asn
        125                 130                 135

aac aca tgc aaa gtc tat tca tct ttt cag tct ttg atg agt gaa tgt      485
Asn Thr Cys Lys Val Tyr Ser Ser Phe Gln Ser Leu Met Ser Glu Cys
    140                 145                 150

tat ggc aaa tat act tct gca aat gaa gac ctc tct aat ttt ggc ctt      533
Tyr Gly Lys Tyr Thr Ser Ala Asn Glu Asp Leu Ser Asn Phe Gly Leu
155                 160                 165                 170

caa att aat act gaa tgg aga tat tct act tct aat acc aac tcc cct      581
Gln Ile Asn Thr Glu Trp Arg Tyr Ser Thr Ser Asn Thr Asn Ser Pro
                175                 180                 185

tgg cac tgg gga ttt ctt ggt gtt tac cga aat ggg gga tac att ttc      629
Trp His Trp Gly Phe Leu Gly Val Tyr Arg Asn Gly Gly Tyr Ile Phe
            190                 195                 200

act tta tca aaa tcg aaa tct gaa acc aaa aac aag ttc att gac ctt      677
Thr Leu Ser Lys Ser Lys Ser Glu Thr Lys Asn Lys Phe Ile Asp Leu
        205                 210                 215

cga ctg aac agc tgg atc aca aga ggg act aga gtt att ttt att gat      725
Arg Leu Asn Ser Trp Ile Thr Arg Gly Thr Arg Val Ile Phe Ile Asp
    220                 225                 230

ttt tcc tta tat aat gct aat gta aat cta ttt tgt att atc aga ttg      773
Phe Ser Leu Tyr Asn Ala Asn Val Asn Leu Phe Cys Ile Ile Arg Leu
235                 240                 245                 250

gtg gca gaa ttc cct gca act gga gga ata ctt act tca tgg cag ttt      821
Val Ala Glu Phe Pro Ala Thr Gly Gly Ile Leu Thr Ser Trp Gln Phe
                255                 260                 265

tac tct gtg aag ctc ctc aga tat gtt agc tac tat gac tat ttt att      869
Tyr Ser Val Lys Leu Leu Arg Tyr Val Ser Tyr Tyr Asp Tyr Phe Ile
            270                 275                 280

gct tcc tgt gaa atc aca ttc tgt att ttt ctt ttt gtc ttc aca aca      917
Ala Ser Cys Glu Ile Thr Phe Cys Ile Phe Leu Phe Val Phe Thr Thr
        285                 290                 295

caa gaa gtc aaa aaa ata aaa gaa ttt aag tct gcc tat ttc aaa agt      965
Gln Glu Val Lys Lys Ile Lys Glu Phe Lys Ser Ala Tyr Phe Lys Ser
    300                 305                 310

att tgg aac tgg cta gaa ttg cta ctt ttg ctg ttg tgt ttt gtg gct     1013
Ile Trp Asn Trp Leu Glu Leu Leu Leu Leu Leu Leu Cys Phe Val Ala
315                 320                 325                 330

gtt tcc ttc aac aca tac tat aat gta caa att ttt ctc tta ctt gga     1061
Val Ser Phe Asn Thr Tyr Tyr Asn Val Gln Ile Phe Leu Leu Leu Gly
                335                 340                 345
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Gln Leu Leu Lys Ser Thr Glu Lys Tyr Ser Asp Phe Tyr Phe Leu Ala
            350                 355                 360

tgc tgg cac att tat tac aat aat ata att gct att acc atc ttt ttt      1157
Cys Trp His Ile Tyr Tyr Asn Asn Ile Ile Ala Ile Thr Ile Phe Phe
        365                 370                 375

gca tgg ata aag ata ttc aaa ttc ata agc ttt aac aag aca atg tct      1205
Ala Trp Ile Lys Ile Phe Lys Phe Ile Ser Phe Asn Lys Thr Met Ser
    380                 385                 390

cag ctg tca tca acc ttg tcc cgt tgt gtt aaa gac ata gta gga ttt      1253
Gln Leu Ser Ser Thr Leu Ser Arg Cys Val Lys Asp Ile Val Gly Phe
395                 400                 405                 410

gcc atc atg ttt ttt ata ata ttc ttt gct tat gcc cag tta gga ttt      1301
Ala Ile Met Phe Phe Ile Ile Phe Phe Ala Tyr Ala Gln Leu Gly Phe
                415                 420                 425

ctt gtt ttt gga tca caa gtt gat gac ttt tcc act ttt cag aat tcc      1349
Leu Val Phe Gly Ser Gln Val Asp Asp Phe Ser Thr Phe Gln Asn Ser
            430                 435                 440

ata ttt gca caa ttt cga att gtt ctt gga gat ttt aat ttt gct ggt      1397
Ile Phe Ala Gln Phe Arg Ile Val Leu Gly Asp Phe Asn Phe Ala Gly
        445                 450                 455

att cag caa gcc aat cct atc ttg gga ccc att tac ttc atc act ttc      1445
Ile Gln Gln Ala Asn Pro Ile Leu Gly Pro Ile Tyr Phe Ile Thr Phe
    460                 465                 470

atc ttt ttt gtg ttc ttt gtc ctg ctg aat atg ttc ttg gca att att      1493
Ile Phe Phe Val Phe Phe Val Leu Leu Asn Met Phe Leu Ala Ile Ile
475                 480                 485                 490

aat gat acc tat tct gaa gtg aaa gct gac tat tca ata ggc aga agg      1541
Asn Asp Thr Tyr Ser Glu Val Lys Ala Asp Tyr Ser Ile Gly Arg Arg
                495                 500                 505

cca gat ttt gaa ctt ggc aaa atg att aaa cag agt tac aaa aat gtt      1589
Pro Asp Phe Glu Leu Gly Lys Met Ile Lys Gln Ser Tyr Lys Asn Val
            510                 515                 520

ctc gag aaa ttc aga ctg aag aaa gct caa aaa gat gaa gac aag aaa      1637
Leu Glu Lys Phe Arg Leu Lys Lys Ala Gln Lys Asp Glu Asp Lys Lys
        525                 530                 535

acc aaa ggc agc gga gat ttg gct gaa caa gcc aga aga gaa ggc ttt      1685
Thr Lys Gly Ser Gly Asp Leu Ala Glu Gln Ala Arg Arg Glu Gly Phe
    540                 545                 550

gac gaa aat gag att caa aac gca gag cag atg aaa aaa tgg aaa gag      1733
Asp Glu Asn Glu Ile Gln Asn Ala Glu Gln Met Lys Lys Trp Lys Glu
555                 560                 565                 570

agg ctt gag aaa aag tat tat tct atg gaa att caa gat gac tac cag      1781
Arg Leu Glu Lys Lys Tyr Tyr Ser Met Glu Ile Gln Asp Asp Tyr Gln
                575                 580                 585

cct gtc act caa gaa gaa ttt cga gat ggc acc aca acc aag tac aaa      1829
Pro Val Thr Gln Glu Glu Phe Arg Asp Gly Thr Thr Thr Lys Tyr Lys
            590                 595                 600

atg aga ttc tct ctg agt gcc tgacaaaacg aatttaagta ccagccaagt        1880
Met Arg Phe Ser Leu Ser Ala
        605

acacacgatg atagcttcaa ggaatacaac tgactttatg atatgaattt tcaaggaacg   1940

tatcttatat ggattttgaa gaatcttgtt tgcttataag aacttcaaga agcctaagct   2000

tggctttaat tttcttgtac tctctgtact cctcaagcac tggaacacga tcctctttct   2060

gggcattcct aggggagaaa ataaaatttg taatgttcta gagatcattt ggaaaaaaag   2120

atccaaaagt tgtcttaata tgagacatac tgttactaaa cataagttca aataaaaagt   2180

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35 40 45

Met Val Asn Pro His Met Tyr Tyr Leu Asn Lys Val Met Ser Ser Leu
50 55 60

Phe Leu Asp Thr Ser Val Pro Gly Glu Glu Arg Thr Asn Phe Lys Ser
65 70 75 80

Ile Arg Ser Ile Thr Asp Phe Trp Lys Phe Met Glu Gly Pro Leu Leu
85 90 95

Glu Gly Leu Tyr Trp Asp Ser Trp Tyr Asn Asn Gln Gln Leu Tyr Asn
100 105 110

Leu Lys Asn Ser Ser Arg Ile Tyr Tyr Glu Asn Ile Leu Leu Gly Val
115 120 125

Pro Arg Val Arg Gln Leu Lys Val Arg Asn Asn Thr Cys Lys Val Tyr
130 135 140

Ser Ser Phe Gln Ser Leu Met Ser Glu Cys Tyr Gly Lys Tyr Thr Ser
145 150 155 160

Ala Asn Glu Asp Leu Ser Asn Phe Gly Leu Gln Ile Asn Thr Glu Trp
165 170 175

Arg Tyr Ser Thr Ser Asn Thr Asn Ser Pro Trp His Trp Gly Phe Leu
180 185 190

Gly Val Tyr Arg Asn Gly Gly Tyr Ile Phe Thr Leu Ser Lys Ser Lys
195 200 205

Ser Glu Thr Lys Asn Lys Phe Ile Asp Leu Arg Leu Asn Ser Trp Ile
210 215 220

Thr Arg Gly Thr Arg Val Ile Phe Ile Asp Phe Ser Leu Tyr Asn Ala
225 230 235 240

Asn Val Asn Leu Phe Cys Ile Ile Arg Leu Val Ala Glu Phe Pro Ala
245 250 255

Thr Gly Gly Ile Leu Thr Ser Trp Gln Phe Tyr Ser Val Lys Leu Leu
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275 280 285

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Lys Glu Phe Lys Ser Ala Tyr Phe Lys Ser Ile Trp Asn Trp Leu Glu
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Leu Leu Leu Leu Leu Leu Cys Phe Val Ala Val Ser Phe Asn Thr Tyr
                325                 330                 335

Tyr Asn Val Gln Ile Phe Leu Leu Leu Gly Gln Leu Leu Lys Ser Thr
            340                 345                 350

Glu Lys Tyr Ser Asp Phe Tyr Phe Leu Ala Cys Trp His Ile Tyr Tyr
        355                 360                 365

Asn Asn Ile Ile Ala Ile Thr Ile Phe Phe Ala Trp Ile Lys Ile Phe
    370                 375                 380

Lys Phe Ile Ser Phe Asn Lys Thr Met Ser Gln Leu Ser Ser Thr Leu
385                 390                 395                 400

Ser Arg Cys Val Lys Asp Ile Val Gly Phe Ala Ile Met Phe Phe Ile
                405                 410                 415

Ile Phe Phe Ala Tyr Ala Gln Leu Gly Phe Leu Val Phe Gly Ser Gln
            420                 425                 430

Val Asp Asp Phe Ser Thr Phe Gln Asn Ser Ile Phe Ala Gln Phe Arg
        435                 440                 445

Ile Val Leu Gly Asp Phe Asn Phe Ala Gly Ile Gln Gln Ala Asn Pro
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Ile Leu Gly Pro Ile Tyr Phe Ile Thr Phe Ile Phe Phe Val Phe Phe
465                 470                 475                 480

Val Leu Leu Asn Met Phe Leu Ala Ile Ile Asn Asp Thr Tyr Ser Glu
                485                 490                 495

Val Lys Ala Asp Tyr Ser Ile Gly Arg Arg Pro Asp Phe Glu Leu Gly
            500                 505                 510

Lys Met Ile Lys Gln Ser Tyr Lys Asn Val Leu Glu Lys Phe Arg Leu
        515                 520                 525

Lys Lys Ala Gln Lys Asp Glu Asp Lys Lys Thr Lys Gly Ser Gly Asp
    530                 535                 540

Leu Ala Glu Gln Ala Arg Arg Glu Gly Phe Asp Glu Asn Glu Ile Gln
545                 550                 555                 560

Asn Ala Glu Gln Met Lys Lys Trp Lys Glu Arg Leu Glu Lys Lys Tyr
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Tyr Ser Met Glu Ile Gln Asp Asp Tyr Gln Pro Val Thr Gln Glu Glu
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Phe Arg Asp Gly Thr Thr Thr Lys Tyr Lys Met Arg Phe Ser Leu Ser
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gcc att cgt tca cgt ctc atc gat act ttc tct ctc att gag cat ttg       96
Ala Ile Arg Ser Arg Leu Ile Asp Thr Phe Ser Leu Ile Glu His Leu
            20                  25                  30

caa ggc ttg agc caa gct gtg ccg cgg cac act atc agg gag tta ctt      144
Gln Gly Leu Ser Gln Ala Val Pro Arg His Thr Ile Arg Glu Leu Leu
        35                  40                  45

gat cct tcc cgc cag aag aaa ctt gta ttg gga gat caa cac cag cta      192
Asp Pro Ser Arg Gln Lys Lys Leu Val Leu Gly Asp Gln His Gln Leu
    50                  55                  60

gtg cgt ttc tct ata aag cct cag cgt ata gaa cag att tca cat gcc      240
Val Arg Phe Ser Ile Lys Pro Gln Arg Ile Glu Gln Ile Ser His Ala
65                  70                  75                  80

cag agg ctg ttg agc agg ctt cat gtg cgc tgc agt cag agg cca cct      288
Gln Arg Leu Leu Ser Arg Leu His Val Arg Cys Ser Gln Arg Pro Pro
                85                  90                  95

ctt tct ttg tgg gcc gga tgg gtc ctt gag tgt cct ctc ttc aaa aac      336
Leu Ser Leu Trp Ala Gly Trp Val Leu Glu Cys Pro Leu Phe Lys Asn
            100                 105                 110

ttc atc atc ttc ctg gtc ttt ttg aat acg atc ata ttg atg gtt gaa      384
Phe Ile Ile Phe Leu Val Phe Leu Asn Thr Ile Ile Leu Met Val Glu
        115                 120                 125

ata gaa ttg ctg gaa tcc aca aat acc aaa cta tgg cca ttg aag ctg      432
Ile Glu Leu Leu Glu Ser Thr Asn Thr Lys Leu Trp Pro Leu Lys Leu
    130                 135                 140

acc ttg gag gtg gca gct tgg ttt atc ttg ctt att ttc atc ctg gag      480
Thr Leu Glu Val Ala Ala Trp Phe Ile Leu Leu Ile Phe Ile Leu Glu
145                 150                 155                 160

atc ctt ctt aag tgg cta tcc aac ttt tct gtt ttc tgg aag agt gcc      528
Ile Leu Leu Lys Trp Leu Ser Asn Phe Ser Val Phe Trp Lys Ser Ala
                165                 170                 175

tgg aat gtc ttt gac ttt gtt gtt acc atg ttg tcc ctg ctt ccc gag      576
Trp Asn Val Phe Asp Phe Val Val Thr Met Leu Ser Leu Leu Pro Glu
            180                 185                 190

gtt gtg gta ttg gta ggg gta aca ggc caa tcg gtg tgg ctt cag ctt      624
Val Val Val Leu Val Gly Val Thr Gly Gln Ser Val Trp Leu Gln Leu
        195                 200                 205

ctg agg atc tgc cgg gtg ctg agg tct ctc aaa ctc ctt gca caa ttc      672
Leu Arg Ile Cys Arg Val Leu Arg Ser Leu Lys Leu Leu Ala Gln Phe
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cgt caa att caa att att att ttg gtc ctg gtc agg gcc ctc aag agc      720
Arg Gln Ile Gln Ile Ile Ile Leu Val Leu Val Arg Ala Leu Lys Ser
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Val Thr Gly Val Tyr Val Phe Ser Glu Tyr Thr Arg Ser Pro Arg Gln
            260                 265                 270

gac ctg gag tac cat gtg ttc ttc tcg gac ctc ccg aat tcc ctg gta      864
Asp Leu Glu Tyr His Val Phe Phe Ser Asp Leu Pro Asn Ser Leu Val
        275                 280                 285

aca gtg ttc att ctc ttc acc ttg gat cat tgg tat gca ctg ctt cag      912
Thr Val Phe Ile Leu Phe Thr Leu Asp His Trp Tyr Ala Leu Leu Gln
    290                 295                 300

gac gtc tgg aag gtg cct gaa gtc agt cgc atc ttc agc agc atc tat      960
Asp Val Trp Lys Val Pro Glu Val Ser Arg Ile Phe Ser Ser Ile Tyr
305                 310                 315                 320

ttc atc ctt tgg ttg ttg ctt ggc tcc att atc ttt cga agt atc ata     1008
Phe Ile Leu Trp Leu Leu Leu Gly Ser Ile Ile Phe Arg Ser Ile Ile
                325                 330                 335

gta gcc atg atg gtt act aac ttt cag aat atc agg aaa gag ctg aat     1056
Val Ala Met Met Val Thr Asn Phe Gln Asn Ile Arg Lys Glu Leu Asn
            340                 345                 350

gag gag atg gcg cgt cgg gag gtt cag ctc aaa gct gac atg ttc aag     1104
Glu Glu Met Ala Arg Arg Glu Val Gln Leu Lys Ala Asp Met Phe Lys
        355                 360                 365

cgg cag atc atc cag agg aga aaa aac atg tca cat gaa gca ctg acg     1152
Arg Gln Ile Ile Gln Arg Arg Lys Asn Met Ser His Glu Ala Leu Thr
    370                 375                 380

tca agc cat agc aaa ata gag gac aga gga gct agt caa caa agg gaa     1200
Ser Ser His Ser Lys Ile Glu Asp Arg Gly Ala Ser Gln Gln Arg Glu
385                 390                 395                 400

agt ttg gac tta tca gaa gtg tct gaa gta gag tct aat tat ggt gcc     1248
Ser Leu Asp Leu Ser Glu Val Ser Glu Val Glu Ser Asn Tyr Gly Ala
                405                 410                 415

act gaa gag gat tta ata aca tct gca tca aaa aca gaa gag acc ttg     1296
Thr Glu Glu Asp Leu Ile Thr Ser Ala Ser Lys Thr Glu Glu Thr Leu
            420                 425                 430

tca aaa aag aga gag tac cag tct tcc tcc tgt gtc tcc tcc aca tcc     1344
Ser Lys Lys Arg Glu Tyr Gln Ser Ser Ser Cys Val Ser Ser Thr Ser
        435                 440                 445

tct tcc tat tct tcc tct tct gaa tcc aga ttt tct gaa tct att ggt     1392
Ser Ser Tyr Ser Ser Ser Ser Glu Ser Arg Phe Ser Glu Ser Ile Gly
    450                 455                 460

cgt ttg gac tgg gag act ctt gtg cac gaa aat ctg ccc ggg cta atg     1440
Arg Leu Asp Trp Glu Thr Leu Val His Glu Asn Leu Pro Gly Leu Met
465                 470                 475                 480

gaa atg gat cag gat gac cgt gtt tgg ccc aga gac tca ctc ttc cga     1488
Glu Met Asp Gln Asp Asp Arg Val Trp Pro Arg Asp Ser Leu Phe Arg
                485                 490                 495

tat ttt gag ttg cta gaa aag ctt cag tat aac cta gag gaa cgt aag     1536
Tyr Phe Glu Leu Leu Glu Lys Leu Gln Tyr Asn Leu Glu Glu Arg Lys
            500                 505                 510

aag tta caa gag ttt gca gtg cag gca ctg atg aac ttg gaa gac aag     1584
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35 40 45

Asp Pro Ser Arg Gln Lys Lys Leu Val Leu Gly Asp Gln His Gln Leu
50 55 60

Val Arg Phe Ser Ile Lys Pro Gln Arg Ile Glu Gln Ile Ser His Ala
65 70 75 80

Gln Arg Leu Leu Ser Arg Leu His Val Arg Cys Ser Gln Arg Pro Pro
85 90 95

Leu Ser Leu Trp Ala Gly Trp Val Leu Glu Cys Pro Leu Phe Lys Asn
100 105 110

Phe Ile Ile Phe Leu Val Phe Leu Asn Thr Ile Ile Leu Met Val Glu
115 120 125

Ile Glu Leu Leu Glu Ser Thr Asn Thr Lys Leu Trp Pro Leu Lys Leu
130 135 140

Thr Leu Glu Val Ala Ala Trp Phe Ile Leu Leu Ile Phe Ile Leu Glu
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Ile Leu Leu Lys Trp Leu Ser Asn Phe Ser Val Phe Trp Lys Ser Ala
165 170 175

Trp Asn Val Phe Asp Phe Val Val Thr Met Leu Ser Leu Leu Pro Glu
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Val Val Val Leu Val Gly Val Thr Gly Gln Ser Val Trp Leu Gln Leu
195 200 205

Leu Arg Ile Cys Arg Val Leu Arg Ser Leu Lys Leu Leu Ala Gln Phe
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Arg Gln Ile Gln Ile Ile Ile Leu Val Leu Val Arg Ala Leu Lys Ser
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Met Thr Phe Leu Leu Met Leu Leu Leu Ile Phe Phe Tyr Ile Phe Ala
245 250 255

Val Thr Gly Val Tyr Val Phe Ser Glu Tyr Thr Arg Ser Pro Arg Gln
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Asp Leu Glu Tyr His Val Phe Phe Ser Asp Leu Pro Asn Ser Leu Val
275 280 285

Thr Val Phe Ile Leu Phe Thr Leu Asp His Trp Tyr Ala Leu Leu Gln
290 295 300

Asp Val Trp Lys Val Pro Glu Val Ser Arg Ile Phe Ser Ser Ile Tyr

305 310 315 320

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Val Ala Met Met Val Thr Asn Phe Gln Asn Ile Arg Lys Glu Leu Asn
340 345 350

Glu Glu Met Ala Arg Arg Glu Val Gln Leu Lys Ala Asp Met Phe Lys
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Arg Gln Ile Ile Gln Arg Arg Lys Asn Met Ser His Glu Ala Leu Thr
370 375 380

Ser Ser His Ser Lys Ile Glu Asp Arg Gly Ala Ser Gln Gln Arg Glu
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Ser Leu Asp Leu Ser Glu Val Ser Glu Val Glu Ser Asn Tyr Gly Ala
405 410 415

Thr Glu Glu Asp Leu Ile Thr Ser Ala Ser Lys Thr Glu Glu Thr Leu
420 425 430

Ser Lys Lys Arg Glu Tyr Gln Ser Ser Ser Cys Val Ser Ser Thr Ser
435 440 445

Ser Ser Tyr Ser Ser Ser Ser Glu Ser Arg Phe Ser Glu Ser Ile Gly
450 455 460

Arg Leu Asp Trp Glu Thr Leu Val His Glu Asn Leu Pro Gly Leu Met
465 470 475 480

Glu Met Asp Gln Asp Asp Arg Val Trp Pro Arg Asp Ser Leu Phe Arg
485 490 495

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